THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JUNE, 1959

ORIGINAL ARTICLES

THE EPIDEMIOLOGICAL APPROACH TO HUMAN ECOLOGY*

By Thomas Francis, Jr., M.D.

PROFESSOR OF EPIDEMIOLOGY AND CHAIRMAN OF DEPARTMENT
UNIVERSITY OF MICHIGAN SCHOOL OF PUBLIC HEALTH
ANN ARBOR, MICHIGAN

It is fitting that the subject of ecology should be considered this year, the centennial of the presentation by Darwin and Wallace of the initial statements of the Origin of Species and Natural Selection. Darwin stressed the complex relations of all animals and plants throughout nature and considered the relation of organism to organism the most important of all relations. The complex web of life, the influence of environment and the struggle for life were prominent features in his naturalistic theory. It is interesting to note, however, that it was his reading of Malthus' "On Population," dealing with human population problems which, according to his own letters, gave him the clue to the concept of natural selection (Darwin[4]).

It was Haeckel, a vigorous supporter and expositor of Darwinism, who in "The History of Creation" in 1868 coined the word Oecology as one of the general laws of biology[11]. "The oecology of organisms: the knowledge of the sum of the relation of organisms to the surrounding outer world, to organic and inorganic conditions of existence; the so-called 'economy of nature,' the correlations between all organisms living together in one and the same locality, their adaptation to their surroundings, their modifications in the struggle for existence, especially the circumstances of parasitism, etc."

Ecology at first concentrated upon the study of plants. Elton, one of the most prominent investigators and writers on animal ecology, points out that much of the earlier work was centered upon the study of adaptations to environment with the idea of proving the theory of natural selection; and on plants because they didn't run away when one wanted to observe them[5]. Ecology, in his view, corresponds to the older terms of Natural History, or Bionomics, constituting the New Natural History[6].

Human ecology can then readily be viewed as the study of the mutual relations of man and his organic and inorganic environment, his adaptations, his struggle for existence, his parasites, and the like. But as Haeckel has

*Talk given at the First Institute on Veterinary Public Health Practice, The University of Michigan, October 6–9, 1958.

said, in ecologic perspective the individual is an abstraction. Consideration of life and its interrelationships, therefore, deals with aggregate or community reactions. (The interrelations between organisms has been called synecology.) Hawley, in his book, reviews the disagreements in the concept of human ecology[12]. He defines it as "the study of the form and the development of the community in human population" and thus "fastens its attention upon the human interdependences that develop in the action and reaction of a population to its habitat." In this view it is primarily a sociological concern and appears to me to be too highly restricted to human relationships. Then, too, human geography is concerned with the influence of environment on man or of man's adaptation to his environment, behavioristically as well as other. Barrows states that geography is the science of human ecology[2]. But Hawley claims that geography deals only with a point in time while ecology is evolutionary. For our needs, however, I shall choose to side with the holistic outlook which can view ecology as a comprehensive con-

Fig. 1.—This represents the melting pot of the numerous components from which a community is cast. It is also the flask in which the various reagents which lead to the support of health or to the compounding of disease are in a dynamic reaction phase.

cept of all relations of all organisms to all their environment, and looks at nature as an integrated system. Subdivisions can be selected according to the nature and needs of the study. The chains of relationship between man and other species become community units of consideration for different purposes. These species networks Audy[1] calls Biocenoses, indicating that they

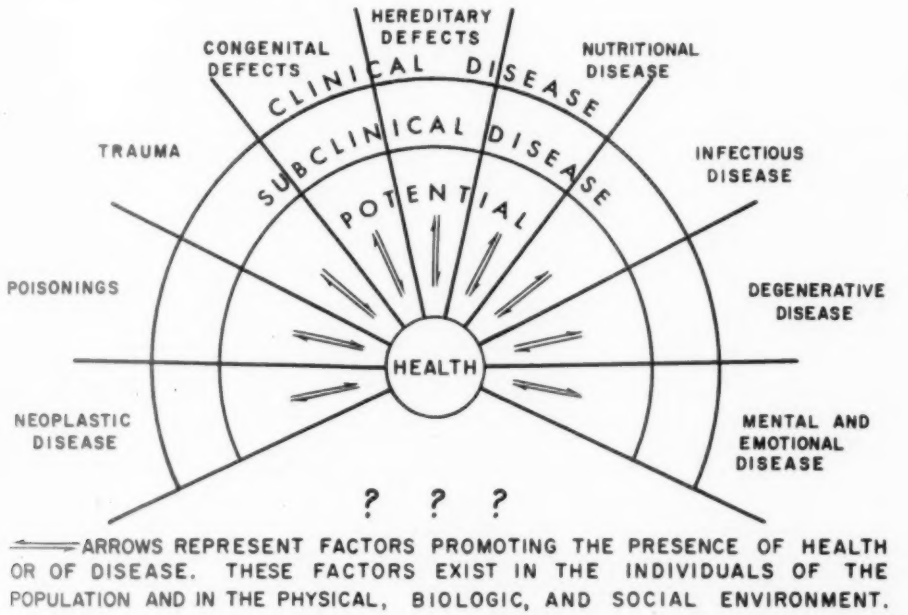


Fig. 2.—Health and Disease: The factorial expert who may look through the field from the position of any of these influences but centering upon man and his status. Need many kinds of study and many kinds of knowledge to give an adequate picture. A composite effect. Each epidemosis may be only a segment, yet man is the detection unit.

function and react as an aggregate system rather than merely as a series of separate actions.

Epidemiology has been variously defined or paraphrased according to the emphasis desired. My own statements have differed in effort to be comprehensive, or brief or even understandable. Thus: a) epidemiology is the study of disease or disability under the natural conditions of its occurrence: b) epidemiology is the study of disease in its natural habitat; c) epidemiology is the study of the laws and factors governing the occurrence of disease or abnormality in a community (population group). These factors include the characteristics of the population, the causative agencies and the biological, physical and social environment (Francis[8a,b]).

W. H. Welch is said to have called epidemiology "the natural history" of disease. Gordon[9] and others have called it "medical ecology." Obviously, what is proposed is that the occurrence of disease is a natural phenomenon, a part of biology, the reaction of man to environmental influences. Essentially epidemiology is a naturalist's viewpoint, clearly ecologic in character, which may consider all relations of all organ-

isms to all their environment as possible factors in the causation of various disorders of man. It is apparent that in most situations the entire universe cannot be explored in detail for finite cause but in the epidemiological community all influences are potentially of determining selective distributions and learning their meaning.

Health may be considered to be adequate structure and function with adequate reserves. This status is constantly exposed to numerous and varied stresses which may reduce reserves to

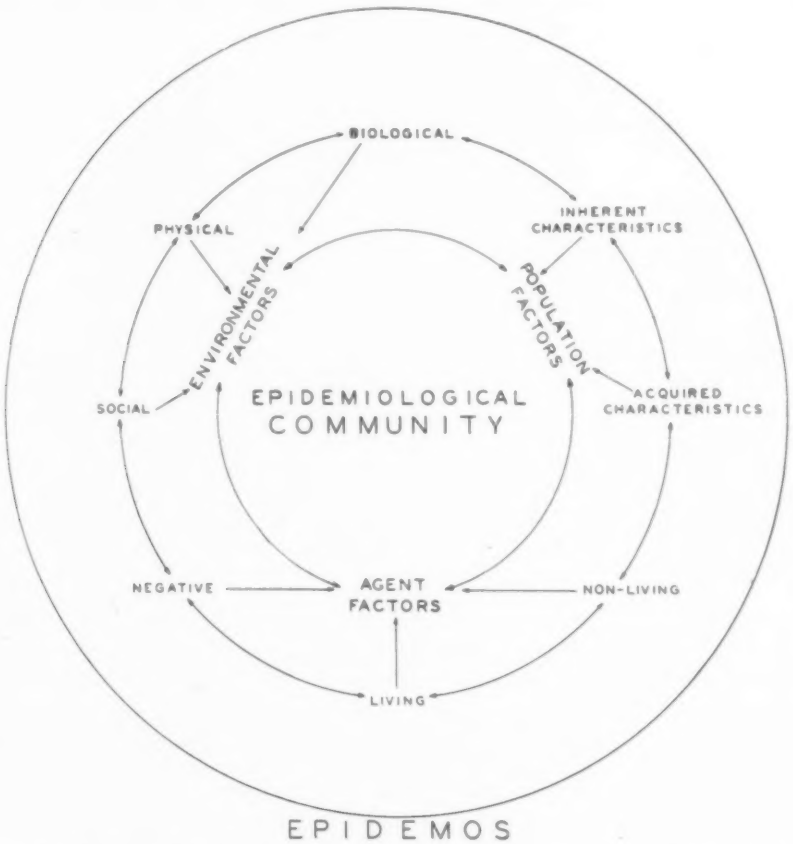


Fig. 3.—Concept of Epidemosis: The complex of influences which may be at play in the development of a disorder.

pathogenic (Fig. 1). Our community is, thus, the pathogenic world in which man is contained. The particular community develops about the actual disease problem from elements of the population and of the environment. The methodology of study is essentially that the extent that tolerance is exceeded and disorder results (Fig. 2).

Perhaps one of the most prominent contributions of epidemiology to human ecology is the concept that disease can serve as a clear indication of maladjustment of man with his environment.

Each disorder then represents a complex epidemiologic unit which constitutes only a segment of the total ecology. We may then refer to the ecologic relationships which lead to causation of the particular disturbance as an *epidemosis*. Although numerous specific epidemoses are recognized, our ability to describe environmental complexes and to measure the effect of them upon health is still primitive (Fig. 3). Nevertheless, the naturalistic view suggests that *man can serve* as a detection system, a biologic trap which catches and displays the effect of a harmful exposure while inviting exploration of his community and his way of life for knowledge of the origins and mode of action of the causative factors; hence to their control and prevention. This is similar to the study of the parasitic load of lower animals which may reveal much of the biologic content of their environments, of their ranges of migration, and of unsuspected pathogenic reservoirs.

Let us now consider certain epidemiological situations in terms of their ecological interpretation (or maybe *vice versa*).

1) Man has not developed competence to live with many closely affiliated forms of life without experiencing harmful effects. The history of disease is a good index of man's progress.

For some of the well-known communicable diseases man apparently provides the entire cycle of reservoir-distributor-recipient. Pertussis, pneumococcal pneumonia, mumps, measles, and typhoid are examples. They appear to be failures in satisfactory adaptation of the host to a parasite with which it has had centuries of experience. If one views the effects of external environment, and what we call predisposing factors, it may be seen that their influences are to provide stresses which strain the effective reserves by exaggerating dosage through crowding, by impairment of physiologic functions through cold, exhaustion or other concomitant insult. But may one suggest that these long associates which still create untoward reactions do in fact have other reservoirs where variants unadapted to man remain or recur? They do not behave like fully domesticated parasites. Basically, they demonstrate that the ecologic factors which aid in their maintenance and transmission have not been adequately changed in man's cultural development over these years.

On the other hand, high frequency of infection without serious manifestations suggests that tolerance or adjustment is well developed as with meningococcus or Type 2 poliovirus. And, in fact, recovery or chronic "carrier" infection represents a rapid adjustment by an adaptable host. Moreover, it can be clearly seen that the impact of these diseases upon human life has been significantly lessened by changes in the way of existence since specific control measures have not been adduced.

2) The appearance of human infectious disease new to a community can be taken as evidence of migratory changes in its assembly of populations. This may indicate excursion by the human, for industrial or other purposes, into well established biologic circuits of other species where it becomes a fifth wheel, unneeded and out of adjustment. The rickettsial biocenoses illustrate this point well. It may be the introduction by man of new biologic populations and their consorts into the community through the medium of his own importations: psittacosis, Q fever, brucellosis, measles in remote islands. Another way is the active migration of insects or small animals or man from affected areas into new zones of operation, bringing to a given community new pathogenic components which

may become established. An increasing incidence thereafter clearly indicates a flourishing new population in this new environment. (Encephalitis in Washington and California.) But in any event a new *epidemosis* is developed, new chains of infection must be delineated and a new element in the ecology is disclosed. In the field of mental disorders, migration into new communities and the social isolation which can result may be important causative factors in precipitating psychoses.

3) In the same manner diseases of other etiology represent new explorations. Man has the great advantage over most of his biological competitors in that he can change and arrange his environment selectively. Many of the changes are made without consideration of its influence upon ecology as a whole. Consequently, new imbalances occur in nature, new migrations, new stresses arise whose influence is unknown. Alterations in mineral content of soil and water, agricultural practices, deforestation, impounding of water may result in variations in disease incidence which become first apparent in the lower animals of the region.

The introduction of new drugs, new industrial processes, new political problems, new foods, new wastes, new weeds, may be reflected in new or increased disease pictures which in turn indicate an altered ecology. Radiation is developing as a new environmental influence whose relationship to disease is being anxiously explored. In this case a potential cause is recognized and its immediate and remote effects are being sought. Its ability to affect the total ecology: social, physical, biological, is sought, using disease and disorder in any of these systems as an index. There must be numerous disorders existing or developing in size which relate to man-made alterations in his ecology but of which man is not aware. (But, in addition, the relationship between common stresses occurring in one period of life and disorders occurring at a much later time has barely been examined). There is need to maintain penetrating study and intelligent observation of new arrangements for the lighting up by ecologic disturbances of latent disorders in the aggregate just as latent disease in the individual may be activated by increased physiological stress. Students of veterinary medicine could well extend their attention more actively to alterations in the ecology of lower animals or for the appearance in them of new disorders which may serve as indices of probable importance to man. One can, nevertheless, emphasize the opportunity to study experimental ecology and disease among natural animal populations under maneuverable conditions.

4) Epidemiological approaches to the knowledge of human ecology are not limited, however, to recognition of influences from man's external biological or physical environment. Some disease phenomena point clearly to disadvantageous relationships in his intimate social environment, in his personal habits, in his intrinsic pattern of behavior. Nutritional practices have changed remarkably with increasing number of additives to food, the use of antibiotics as preservatives, the chemical processes of refinement or the distortion of a reasonable diet by the pressures for social esteem (white bread, polished rice, excessive fat). The increased incidence of coronary disease, of cancer of the lung, call attention to harmful influences of man's own selection regardless of the primary etiologic factor. Cochran has ventured the suggestion that the alteration in the pattern of paralytic poliomyelitis may be an influence not merely of sanitary improvement but related as well to re-

moval from the diet of numerous natural antibiotics which may inhibit viral growth[3]. Another example: when epidemiological studies reveal a strong genetic determinant in the occurrence of a disease, it indicates the disadvantages to human ecology of biologically unselective mating. I scarcely need to mention the endemic and epidemic results of social maladjustments so prominently before us today.

EPIDEMIOLOGICAL CONSTANTS AND THEIR ECOLOGICAL USE. In epidemiological investigation the characteristics of the population involved are of fundamental importance. The selective localizations of affected and unaffected persons in these populations is mapped. From each of these, information of ecological value is obtained. The incidence of many acute infections is greatest in childhood, indicating that the older segment of the population has become adapted to that exposure by its immune mechanisms. On the other hand, the lower case fatality in the younger population, as in typhus, pneumonia, indicates a greater tolerance and resiliency. Or in other conditions differentials in exposures may thus be brought to light or it may be only that the abnormality requires time for its development. Variation in incidence of disease prevalence among different socio-economic groups clearly points to accompanying differences in their general ecology and exposures. Differences in distribution by sex point to differences in exposure because of habits, occupations, or to differences in physiological competence. Why is disseminated lupus especially prominent in the female of 20 to 40?

The geographic distribution of a disorder indicates much more than position. The different areas of the world can be characterized by their complement of diseases, calling attention, as Hippocrates pointed out, to airs, waters and places, the idea of place infection dependent upon the constitution of the community. It is here appropriate to point out that geographic location may relate primarily to inbred characteristics or habits of the human population, to the dynamics of its animal ecology, to mineral excesses or deficiencies; in short, to *epidemoses* involving a web of ecological influences which interfere with the maintenance of adequate structure and function with adequate reserves.

Because of the changing universe about us, I find it difficult to visualize a world without disease and maladjustment. The atomic age, the exploration and population of space, of itself will create new epidemiological and ecological boundaries. Epidemiology is basically an investigative field representing the application of the scientific method to problems of population groups generally. Various points of reference may be taken in mapping out the general ecology of man. Epidemiology thus moves with disease and disorder as its index. Its approach to human ecology is to detect, to measure, to understand the harmful influences which impair the relationship of man with his environment. It is a study of pathogenesis, not just observation. While trying to obtain adequate measurement of these stresses, the effort should lead to the better definition of health, to the better design of procedures for maintenance of health and for the prevention of its deterioration. Never before has the social climate blended so well with the biological and physical approaches to make population investigations possible and popular. But in undertaking such studies one must guard against those harmful influences which may lead to popular but dubious conclusions and to give attention to the constant need for con-

trolled data which permit valid interpretations and conclusions.

Alan Gregg said "Practice does not make perfect"[10] but rather as Stephen Vincent Benet expressed himself, "It is worthy to assemble facts, to put fact in the face of legend, to investigate impartially, to shed new light on old things,"[7] but we must also be alert to the search for new correlations and to the understanding of new influences. This is heady stuff.

REFERENCES

1. **Audy, J. R.:** Tr. Roy. Soc. Trop. Med. & Hyg., **52**, 308, 1958.
2. **Barrows, H. H.:** Ann. Assn. Am. Geographers, **13**, 1, 1923.
3. **Cochran, K. W.,** and **Lucas, E. H.:** Sixth Annual Antibiotics Symposium, in press.
4. **Darwin, F.** (Ed.): The Life and Letters of Charles Robert Darwin. New York: Appleton-Century-Crofts, Inc., p. 68, 1919.
5. **Elton, C.:** Animal Ecology. London: Sidgwick and Jackson, Ltd., 1927.
6. Encyclopedia Brittanica: Animal Ecology, **7**, 915–924, 1947.
7. **Fenton, C.:** Atlantic Monthly, **202**, No. 3, 45, 1958.
8. **Francis, T., Jr.:** (a) The Teaching of Epidemiology. Proc. First World Conference on Medical Education, London, 1953; (b) J. Med. Education, **29**, No. 10.
9. **Gordon, J. E.:** The History of American Epidemiology. St. Louis: C. V. Mosby Co., p. 116, 1952.
10. **Gregg, A.:** Univ. of Michigan Med. Bull., **22**, 93, 1956.
11. **Haeckel, E.:** The History of Creation. Revised English translation by **E. R. Lankester**, 1874 of German Edition, 1868. New York: D. Appleton Co., Vol. II, p. 354, 1874.
12. **Hawley, A. H.:** Human Ecology. New York: Ronald Press Co., Chap. 4, pp. 66–74, 1950.

SUMMARIO IN INTERLINGUA

Aspecto Epidemiologic De Ecologia Human

Ecologia human es reguardate como le studio del relationes mutual inter le homine e su ambiente organic e inorganic, su adaptationes, su lucta de existentia, su parasitos, etc. Illo es un disciplina que se occupa minus del homine qua individuo que qua aggregato o communitate. Epidemiologia es un phase special de ecologia in que morbo o disordine es le centro del interesse. Omne le influentias in le communitate es potentialmente nocive al homine. Ergo, maladia es un indication de maladjustamento inter le homine e su ambiente. Omne disordine es alora un complexe entitate epidemiologic que constitue solmente un segmento del ecologia total. Le totalitate del relationes que duce al causation de un disturbation particular pote esser appellate un epidemiosis. Le differente characteristicas del problemas de morbo in le communitate indica differente formas de maladaptation del homine a su ambiente. Illos pote indicar que in le curso de multe seculos le homine ha facite nulle progresso in su association con organismos que causa le epidemias con ancianissime historias. Le apparition de un nove disordine indica alterationes in le processo migratori in le communitate, o illo indica nove expositiones, nove methodos, nove alterationes in le stato del communitate. Altere disturbationes signala le facto que le modo de viver del homine mesme es continuemente nocive a causa de su maladjustamento. Un desiderato de urgentia, per consequente, es continuate investigationes que visa a determinar causa, pathogenese, e subjugation. Le application epidemiologic del methodo scientific pote esser de grande valor.

COMPARISON OF THE GRANULOMA PRODUCING CAPACITY OF NORMALS AND SARCOID GRANULOMA PATIENTS: EXPERIMENTAL ANALYSIS OF THE SARCOID DIATHESIS THEORY*

By Harry J. Hurley, M.D., D.Sc.(Med.)†
ASSOCIATE IN DERMATOLOGY

AND

Walter B. Shelley, M.D., Ph.D.
PROFESSOR OF DERMATOLOGY

(From the Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania)

Sarcoid granulomas present a distinctive histopathological picture. They consist of nests or tubercles of virtually pure epithelioid cells, with little or no central necrosis, a minimum of associated inflammatory cells, and occasional giant cells (Fig. 1). As such they may be differentiated from classical tuberculoid and foreign body or phagocytic granulomas (Fig. 2), although study of serial sections of the tissue may be necessary in some cases. They are further characterized by gradual, undramatic growth and development, and once developed, by relative stability and recalcitrance to treatment. Such sarcoid granulomas are seen as the classical picture in such disorders as sarcoidosis, berylliosis, tuberculoid leprosy, silicon, and zirconium deodorant granulomas, and have been described occasionally in other conditions which usually result in different tissue reactions, such as histoplasmosis, cryptococcosis, syphilis, tuberculosis and reactions to foreign bodies (Birnstein and Leider[1], Bjornstad[2], Heller *et al.*[4], Israel *et al.*[7], Refvem[12]). The precise mechanisms responsible for the development of these sarcoid granulomas have remained obscure, although in the case of the zirconium deodorant granulomas, at least, there is strong experimental evidence indicating that they are the result of an allergic hypersensitivity to the zirconium which manifests itself as a sarcoid granuloma (Shelley and Hurley[13]).

One of the more popular theories regarding the pathogenesis of sarcoidosis and sarcoid granulomas in general, is that such tissue reactions are due to an inherent sarcoid mode of reaction in these patients, that is, they are the result of a "general predisposition, congenital or acquired, on the part of certain individuals to respond with a sarcoid granuloma to a variety of stimuli which in other persons would provoke a qualitatively different (non-granulomatous) response" (Israel and Beerman[6], Kooij and Gerritsen[9]). Individuals with this predisposition or reactivity have been said to possess a sarcoid diathesis or "terrain sarcoidique."

The theory of the sarcoid diathesis is not of recent origin. A long list of observers have seen fit to support it (Darier[3], Kooij[8], Kooij and Gerritsen[9], Kyrle[10], Oppenheim[11], Volk[14]). Within

*This work was supported by a research grant (E–2445) from the Division of Research Grants, U.S. Public Health Service.

†Present address: Hahnemann Medical College, Philadelphia, Pennsylvania.

the past year, even, new reports have appeared, notably by Kooij, emphasizing the validity of this concept[8]. The latter author in presenting his data makes no attempt to explain the sarcoid diathesis in such patients, that is, whether it is congenital or acquired, and ignores the convincing experimental evidence that at least one variety of sarcoid granuloma, for example, the zirconium deodorant granuloma, is the result of an acquired, specific (allergic) hypersensitivity. The result is that, in his opinion, all sarcoid granulomas, regardless of apparent causal relationship to infectious disease processes or foreign material, are lumped together and defined simply as the result of a sarcoid mode of reaction. It is probable that such a theory, in its broadest sense, could hardly be considered incorrect. However, it is assumed that most proponents of the sarcoid diathesis theory relate it to a tissue defect or alteration, presumably reticuloendothelial, and most often congenital, which is not the result of the usual disease mechanisms, such as allergy, reaction to inflammation, and the like, known today. The issue is, then, whether such a tissue predisposition is present in patients who develop sarcoid granulomas. It would seem that a fundamental axiom of the sarcoid diathesis theory provides that such people would react distinctively, qualitatively or quantitatively, or both, to a variety of granulomagenic stimuli. In short, they should be able to form granulomas more easily and of greater size than do normals without such a predisposition.

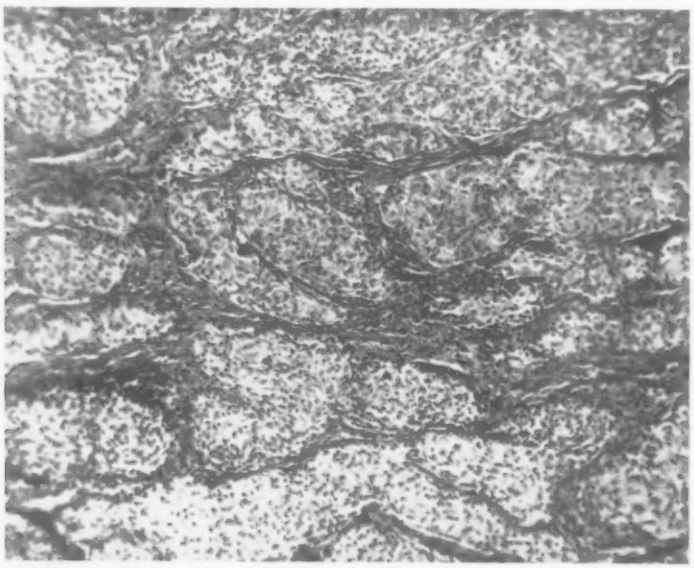
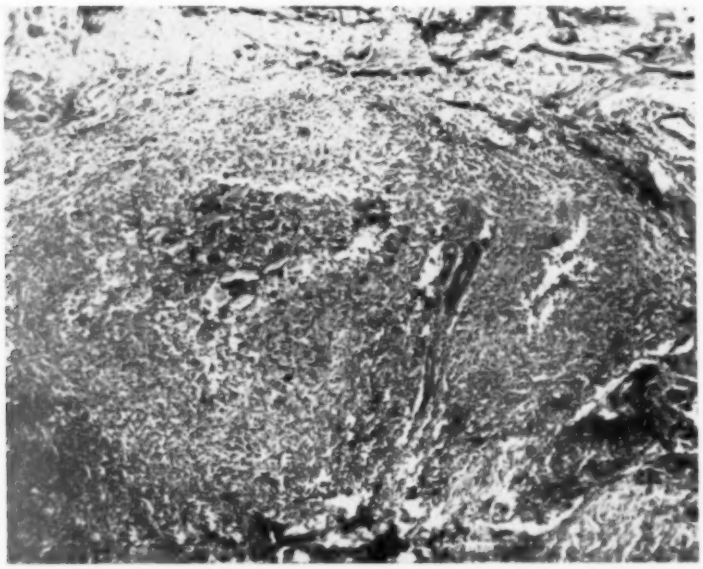


Fig. 1.—Typical sarcoid granuloma in human skin. This lesion represents an axillary papule of a patient with zirconium deodorant granulomas of several months' duration. Above histopathological picture, consisting of nests of virtually pure epithelioid cells without central necrosis and with a minimum of associated inflammatory cells, is characteristic of sarcoid granulomas. Mag. × 105.

As part of a broad investigative pro-



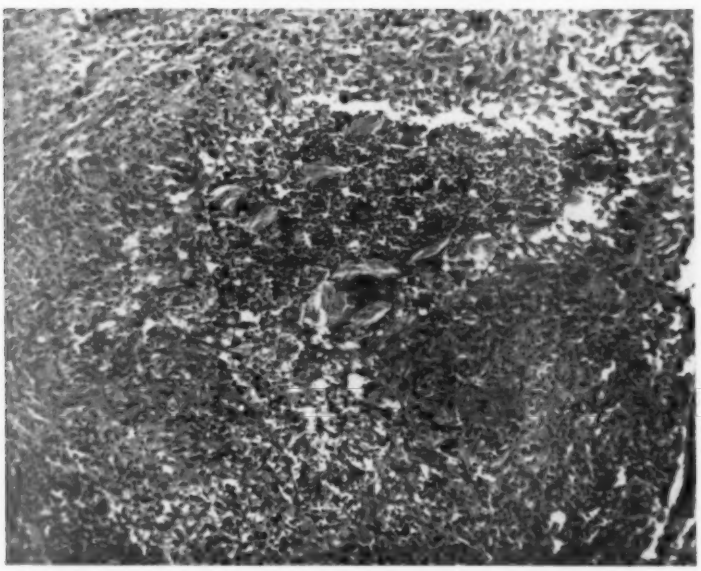


Fig. 2.—Foreign body granuloma in human skin. The above granulomatous lesion was produced by 0.05 ml. of 0.2 M pure sodium stearate injected intradermally 3 weeks earlier. Note central zone containing particles of foreign sodium stearate, macrophages and inflammatory cells. Surrounding this is epithelioid granulomatous infiltrate. Contrast this type of granuloma with the sarcoid granuloma shown in Fig. 1. Upper mag. × 65. Lower mag. × 105.

gram involving granuloma production in human skin over the past few years, we have examined critically the theory of the sarcoid diathesis as it relates to sarcoidosis and zirconium deodorant granuloma patients. Our study consisted of a comparison of the granuloma-producing capabilities of normal human subjects and those with sarcoidosis or the zirconium deodorant granuloma. The granulomagenic stimuli included *sodium stearate*, a soap of high granuloma-producing capacity (Hurley and Shelley[5]), *beryllium*, *silicon* and *zirconium*, all of which have been known to induce sarcoid granlomas in certain patients (Israel and Beerman[6], Shelley and Hurley[13]).

Material and Methods. Human subjects, the majority of whom were males, ranging in age from 19 to 62 years, were used in this study. They included 300 normal male volunteers without evidence of any disease state or other abnormality of significance after a careful history, physical examination, and a battery of laboratory studies. One hundred eight-six of these subjects were Negroes; the rest were white. Thirty-five patients with clinical and laboratory evidence of sarcoidosis and 6 patients with proven axillary zirconium granulomas were also used. The latter patients were shown to possess generalized cutaneous allergic hypersensitivity to any water soluble zirconium salt. This hypersensitivity was in the form of a sarcoid granuloma reaction and was proved after a variety of studies, including histological and spectrographic analysis of the tissue and specific skin testing to zirconium and a host of other metals (Shelley and Hurley[13]).

The following substances were employed in skin test injections:

1. Sodium stearate (ultra-pure)*, 0.2 M, in sterile distilled water, in a dose of 0.05 ml. This suspension was manually ground with a glass homogenizing rod to produce a homogeneous preparation as described previously (Hurley and Shelley[5]) and injected into the skin of the subject. The skin of the back and forearm was used as test sites in the different subjects throughout the study.

2. A series of 73 metals and elements of the periodic table as indicated in Table 1 below. All of these were used as water soluble salts in a concentration of 1:10,000, with the exception of bismuth, silicon, silver, and thallium, which were used as insoluble suspensions.

3. Whole blood, secured from each patient and then immediately injected in a dose of 0.05 ml. into the forearm of the same patient.

TABLE 1.—ELEMENTS USED IN SKIN TESTS†

Aluminum	Erbium	Magnesium	Scandium
Antimony	Europium	Manganese	Silicon
Arsenic	Fluorine	Mercury	Silver
Barium	Gadolinium	Molybdenum	Sodium
Beryllium	Gallium	Neobium	Strontium
Bismuth	Germanium	Neodymium	Sulfur
Boron	Gold	Nickel	Tantalum
Bromine	Hafnium	Nitrogen	Tellurium
Cadmium	Holmium	Oxygen	Terbium
Calcium	Hydrogen	Palladium	Thallium
Carbon	Indium	Phosphorus	Thulium
Cerium	Iodine	Potassium	Tin
Cesium	Iridium	Praesodymium	Titanium
Chlorine	Iron	Rhenium	Tungsten
Chromium	Lanthanum	Rhodium	Vanadium
Cobalt	Lead	Rubidium	Ytterbium
Copper	Lithium	Ruthenium	Yttrium
Dysprosium	Lutetium	Samarium	Zinc
			Zirconium

*This substance was specially prepared by the Applied Science Laboratories, State College, Pennsylvania. It had a purity of 99.5% or better.

†See text under **Material and Methods.**

The number of subjects studied with each of these compounds is indicated in Table 2 below.

TABLE 2.—SUMMARY OF TYPES OF PATIENTS STUDIED WITH THE VARIOUS SKIN TESTS

	Normals	*Sarcoidosis*	*Zirconium Granulomas*
Sodium stearate	300	15	6
Metals (73)	55	35	6
Whole blood, homologous	25	5	4

Observations were made on the skin test areas daily for 2 weeks and then at weekly intervals through 12 weeks. Surgical biopsies were taken as indicated, and the tissue was fixed in formalin and stained with routine hematoxylin and eosin or by the van Gieson technique.

Results. 1. In response to the intradermal injection of sodium stearate, 286 of 300 normal male subjects formed a small papule which persisted through 2 weeks. Two hundred forty-two of these men showed a persistent papule at 3 weeks, and 168 had a residual papule at 4 weeks. Most of the papules resolved clinically within 6 to 7 weeks. In no subject was a papule evident beyond 8 weeks. Biopsies of representative lesions were taken and included at least 100 such biopsy specimens at various periods. Histologically, in the early 2 week papules an early foreign body granuloma was seen, with insoluble stearate in variable quantities, round cell infiltration with some polymorphonuclear cells, and diffuse epithelioid cell change. It was clearly an epithelioid granulomatous infiltrate. Such epithelioid cells were arranged in broad sheets or bands and not in nests or tubercles as one classically sees in the sarcoid granuloma. By 3 weeks the granuloma had become less inflammatory and more stearate had been ingested by the reticuloendothelial cells producing larger sheets of epithelioid cells. Some giant cells were also seen. These were mostly of the foreign body variety, but included all morphological types. At 4 to 5 weeks, in those with a persistent papule clinically, the granulomatous change was better developed with less stearate visible. In those in whom a palpable lesion was not present at this time, there was still histological evidence of a local granuloma, but it was reduced in size. In some patients with a palpable lesion at 4 to 5 weeks, there was relatively little phagocytosis of the sodium stearate, and indeed much of what we actually felt was the sodium stearate mass itself, although in all cases on the peripheral rim of the tissue some epithelioid cell activity was seen.

In the sarcoidosis patients, injected with sodium stearate, all 15 presented a palpable lesion through 2 weeks. Eleven of the 15 had a lesion still palpable clinically at 3 weeks, and 8 of the 15 had lesions which lasted to 4 weeks. Beyond this time all lesions gradually resolved and were gone within 6 to 8 weeks in all of these 15 patients with sarcoidosis. Histologically their reactions resembled exactly the spectrum of reaction seen in the normals to sodium stearate. There was no qualitative or quantitative variation, and there was no formation of typical sarcoid granulomatous lesions.

In the 6 patients with zirconium deodorant granulomas, all 6 presented palpable lesions through 2 weeks, and 5 of the 6 still had lesions palpable at 3 weeks. Three of the 6 had persistent palpable injection sites at 4 weeks, although beyond this time the lesions gradually resolved to disappear at the 6 to 8 week period. Again their histological patterns were indistinguishable from those seen in the normal male volunteers as described above to sodium stearate. There was no qualita-

tive or quantitative difference in reactivity.

2. With the metals and elements of the periodic table no granulomatous reactions were seen in any of the normal subjects tested, in any of the sarcoidosis patients tested, nor in any of the latter group where zirconium salts were used. In this single specific instance, that is, at the zirconium skin test site in the zirconium granuloma patients, a local granuloma appeared at about 3 weeks and persisted through several months. Biopsy of these sites after 3 to 4 weeks revealed a mature granuloma which after several months has been shown to resolve gradually. This granuloma was typically sarcoid in nature, that is, it consisted of nests of virtually pure epithelioid cells with no central necrosis and a minimum of associated inflammatory cells as described earlier.

3. The injection of homologous whole blood in all 3 groups of patients failed to produce a persistent papule beyond a few days. Biopsy of these sites early and late (3 to 4 weeks) revealed only normal tissue or minimal perivascular round cell infiltration. There was no evidence of any granulomatous reaction.

Discussion. The above study has shown that none of the patients with diseases characterized by sarcoid granuloma formation, that is sarcoidosis and zirconium deodorant granulomas, reacted unusually in either a qualitative or quantitative sense to any of the granulomagenic stimuli employed. Some of these granuloma-producing substances had been known to produce granulomas quite regularly, namely, sodium stearate, zirconium, beryllium and silicon. No sarcoid granulomas were seen, except in the case of the zirconium deodorant granuloma patients in their skin test injections to the zirconium salt itself. Although there was some variation in the ability of some patients to react to sodium stearate, which apparently reflects a variation in the ability to phagocytize this lipid (Hurley and Shelley[5]), there was no sarcoid granuloma formed by any of the sarcoidosis or zirconium deodorant granuloma patients or the normal subjects. Indeed there was no unusual response by these patients to the sodium stearate, that is, they did not form a larger granuloma than did the normals, nor one of longer duration. Similarly with the zirconium, beryllium, silicon and all of the other elements, as well as the homologous whole blood, there were no granulomatous reactions seen except in the case of the zirconium deodorant granuloma patients to the zirconium salts themselves. This would seem to indicate that such patients lack any predisposition to form granulomas more readily, or granulomas of greater size or duration. Moreover, they failed to react distinctively in a qualitative sense, that is, they did not induce sarcoid granulomas to an agent (sodium stearate) which, in normal patients, excites a foreign body type of granuloma. Rather since only the zirconium granuloma patients formed a sarcoid granuloma, and only to the specific substance zirconium, this study indicates that a great specificity of the sarcoid granuloma tissue reaction pattern is present. In sarcoidosis a specific granulomagenic agent, possibly an antigen, has not been isolated. In those cases of histoplasmosis, tuberculosis, syphilis, and so forth, in which sarcoid granulomas are occasionally seen and which simulate sarcoidosis histologically, it is probable that some component of the organisms themselves is responsible for the sarcoid granuloma reaction. It is also possible that such bacterial components may be acting antigenically just as does the zirconium in zirconium granu-

loma patients to yield the allergic granuloma described. From this study, it would seem that the theory of the sarcoid diathesis and its importance in the production of sarcoid granulomas at least in sarcoidosis and the zirconium deodorant granuloma, would have to be rejected. This is further supported by reports in the literature indicating that sarcoidosis patients failed to react distinctively or at all to a host of foreign materials including catgut, talc, aleuronate, silicates, milk, collodion, India ink, and the like (Refvem[12]). Rather it is probable that the search for a specific granulomagenic agent or antigen should be continued in all cases of sarcoidosis as well as in those other conditions which elicit the sarcoid granuloma tissue reaction pattern.

It is worth mentioning that the injections given in this study were made at an intradermal and not a subcutaneous level. As has been shown on many occasions, the injection of a variety of materials into the subcutaneous tissue will often result in the release of lipids secondarily as a result of tissue injury and necrosis. These lipids then probably result in the production of local granulomas. However, it should be stressed that histologically these granulomas are not of the sarcoid variety, but are rather of the foreign body or phagocytic type similar to what is seen after sodium stearate.

It should be noted further that there was a variation in the capacity of various normal subjects, as well as those people with sarcoidosis and other zirconium granulomas to form a granulomatous reaction, of the foreign body type, to sodium stearate. However, this variation was not a qualitative one, but was quantitative in nature. Less epithelioid cells and more stearate were visible in some people while more epithelioid cells, representing greater phagocytosis and earlier destruction of the foreign material, and less insoluble stearate were seen in others. As we have stated, this would appear to reflect a variation in the ability of the macrophages to ingest and metabolize the sodium stearate.

Conclusions. 1. In an attempt to evaluate the significance of the theory of the sarcoid diathesis in the production of sarcoid granulomas, a comparison of the granuloma producing capacity of 300 normal male subjects was compared with that of 35 patients with sarcoidosis and 6 patients with zirconium deodorant granulomas. Both of these conditions formed classical sarcoid granulomas regularly. The granulomagenic stimuli employed were sodium stearate, beryllium, silicon, zirconium, and a host of other elements as well as homologous whole blood. Intradermal skin test injections of all these substances were given and compared clinically and histologically.

2. There was no variation, qualitatively or quantitatively, between the 300 normal subjects and those of the patients with sarcoidosis or the zirconium deodorant granulomas to any of the stimuli employed with one exception. This proved to be the water soluble zirconium salt in the case of the zirconium deodorant granuloma patients. In this singular instance a local granulomatous papule, typically sarcoid histologically, was seen to develop at 3 to 4 weeks and persist for several months, as is consistent with the pathogenesis of this type of granuloma as discussed within.

3. As a result of these studies, at least in these 2 types of sarcoid granulomas, namely sarcoidosis and zirconium deodorant granuloma, we would doubt that the sarcoid mode of reaction is operative. Rather as in the case in these 2 conditions and probably in the case of other varieties of sarcoid

granulomas, a specific granulomagenic substance is responsible for the production of this unusual tissue response. Continued search for such specific granulomagenic substances is indicated.

REFERENCES

1. **Birnstein, E.,** and **Leider, M.:** J. Invest. Derm., **15,** 75, 1950.
2. **Bjornstad, R. T.:** Acta tuberc. Scandinav., **22,** 142, 1948.
3. **Darier, J.:** Bull. Soc. Franc. Derm. & Syph., **41,** 999, 1934.
4. **Heller, S., McLean, R. A., Campbell, C. G.,** and **Jones, I. H.:** Am. J. Med., **22,** 986, 1957.
5. **Hurley, H. J.,** and **Shelley, W. B.:** J. Invest. Derm., in press.
6. **Israel, H.,** and **Beerman, H.:** Excerpta Med. Derm. & Vener. (Amsterdam), **10,** 3, 1956.
7. **Israel, H., DeLamater, E., Sones, M., Willis, W. B.,** and **Mirmelstein, A.:** Am. J. Med., **12,** 252, 1952.
8. **Kooij, R.:** Dermatologica, **117,** 336, 1958.
9. **Kooij, R.,** and **Gerritsen, T.:** Ibid., **116,** 1, 1958.
10. **Kyrle, J.:** Arch. Derm. & Syph. (Berlin), **125,** 481, 1920.
11. **Oppenheim, M.:** Ibid., **119,** 120, 1914.
12. **Refvem, O.:** Acta med. Scandinav., **49,** (Suppl. 294), 11, 1954.
13. **Shelley, W. B.,** and **Hurley, H. J.:** Brit. J. Derm., **70,** 75, 1958.
14. **Volk, R.:** Tuberculose der Haut. Handbuch der Haut und Geschlectskrankheiten, Berlin: Julius Springer, Vol. 1, pp. 1-686, 1931.

SUMMARIO IN INTERLINGUA

Comparation Del Capacitate Granulomatogene De Subjectos Normal E De Patientes Con Granuloma Sarcoide: Analyse Experimental Del Theoria De Un Diathese Sarcoide

1. In un effortio de evalutar le signification del theoria de un diathese sarcoide in le production de granulomas sarcoide, le capacitate granulomatogene de 300 masculos normal esseva comparate con illo de 35 patientes con sarcoidosis e de 6 patientes con granuloma per deodorantes a zirconium. In ambe iste conditiones, classic granulomas sarcoide esseva formate regularmente. Le stimulos empleate esseva stearato de natrium, beryllium, silicium, zirconium, e un extense batteria de altere elementos si ben como etiam homologe sanguine integre. Injectiones intradermal esseva usate in tests cutanee con omne le mentionate substantias, e le resultatos esseva comparate clinica- e histologicamente.

2. Esseva constatate nulle variation—qualitative- o quantitativemente—inter le 300 subjectos normal e le patientes con sarcoidosis o illes can granulomas per deodorantes a zirconium in lor reaction al varie stimulos usate—con un exception. Iste exception esseva le hydrosolubile sal de zirconium in le caso del patientes con granuloma per deodorantes a zirconium. In iste caso specific, un local papula granulomatose—typicamente sarcoide in su charactersticas histologic—se disveloppava al fin de 3 a 4 septimanas e persisteva durante plure menses, de accordo con le pathogenese de iste typo de granuloma como illo es discutite in le texto complete de iste articulo.

3. Super le base del resultatos de iste studios, e al minus con respecto a iste 2 typos de granuloma sarcoide—*i.e.* sarcoidosis e granuloma per deodorantes a zirconium—nos trova dubitose le applicabilitate del concepto de un "terreno sarcoidic" como base del reaction. Nos opina plus tosto que in le caso de iste 2 conditiones e probabilemente in le caso de altere varietates de granuloma sarcoide, un specific agente granulomatogene es responsabile pro le production de iste inusual reaction histologic. Le continuate effortio de identificar tal specific agentes granulomatogene es indicate.

EFFECT OF FOOD ON THE ABSORPTION OF ERYTHROMYCIN PROPIONATE, ERYTHROMYCIN STEARATE AND TRIACETYLOLEANDOMYCIN

By Hans A. Hirsch, M.D.

RESEARCH FELLOW IN MEDICINE, HARVARD MEDICAL SCHOOL AND THORNDIKE MEMORIAL LABORATORY

AND

Maxwell Finland, M.D.*†

ASSOCIATE PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL; ASSOCIATE DIRECTOR, THORNDIKE MEMORIAL LABORATORY, AND PHYSICIAN-IN-CHIEF, FOURTH MEDICAL SERVICE, BOSTON CITY HOSPITAL

(From the Thorndike Memorial Laboratory, Second and Fourth (Harvard) Medical Services, Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston, Massachusetts)

In a previous study (Kunin, Pryles and Finland[21]) it was shown that triacetyloleandomycin produced antistreptococcal and antistaphylococcal activity in the serum of normal men and in children comparable to that produced by equivalent amounts of erythromycin. The adults in this study were given the triacetyloleandomycin in the form of 2 capsules each containing 250 mg. base equivalent and the erythromycin was given as 2 specially coated tablets each containing 250 mg. of erythromycin base and the comparisons were made on the basis of single doses given ½ to 1 hour before breakfast. The children each received the base equivalent of 10 mg. per kg. every 8 hours in the form of suspensions of erythromycin ethyl carbonate and triacetyloleandomycin, at least 2 of the 3 daily doses being given soon after a meal.

Soon after that study was completed, the new monopropionyl ester of erythromycin was made available. Oral administration of single 500 mg. doses of this ester in 2 capsules to some of the same normal subjects used in that study yielded higher levels of antibacterial activity than had been obtained from the equivalent amounts of either the capsules of triacetyloleandomycin or the coated tablets of erythromycin base. A further crossover study (Hirsch, Kunin and Finland[14]) was, therefore, carried out in which 8 other normal men were given single doses of 2 capsules of erythromycin propionate and triacetyloleandomycin containing 500 base equivalents of each 2 hours before breakfast. The antistreptococcal and antistaphylococcal activity produced in the serum was measured by a twofold dilution method and, in addition, the concentration of antibiotic in the serum was measured by an agar cup-plate, diffusion method with *Sarcina lutea* as in standard antibiotic assays (Grove and Randall[11]). The results of the latter tests were expressed numerically in terms of activity equivalents calculated as both erythromycin and oleandomycin by comparison with standard solutions of these respective bases. In this study the antistaphylo-

*With the technical assistance of Clare Wilcox and Ann Najarian.
†Aided by a grant (E–23) from the National Institutes of Health.

coccal and antistreptococcal activity at each interval, the "peak" activity and the "total" activity derived from each dose as judged from the maximum inhibiting dilutions of the serum for the test strains were several times greater after the dose of erythromycin propionate than after the dose of triacetyloleandomycin.

In the second study, the average concentrations of oleandomycin at 1, 2 and 4 hours and the peak concentrations of oleandomycin achieved after the dose of triacetyloleandomycin were slightly greater than the corresponding concentrations of erythromycin in serum after the dose of erythromycin propionate, but the reverse was true at subsequent intervals after the doses and the "total" activity produced by each dose, when calculated in terms of "microgram-hours" of the homologous antibiotic, was the same. However, when the levels of antibiotic in the serum were compared on the basis of equivalent activity of either erythromycin or oleandomycin, the average levels of serum at all intervals, the peak levels and total activity were several times greater after the dose of erythromycin propionate than after the dose of triacetyloleandomycin. The great importance of expressing activity in terms of the same standard of reference in comparing the value of different antibiotic preparations was thus clearly demonstrated.

The present paper reports 2 additional studies. In the first, the levels of antibiotic activity produced in the blood of the same normal subjects during continuous administration of erythromycin propionate and triacetyloleandomycin were compared. Because the results of this study suggested that most of the previously demonstrated advantage of erythromycin propionate was lost, and since each of the doses was given after meals, a second study was done in which direct comparisons in the same individuals were made of the antibacterial activity in serum resulting from the same amounts of the antibiotics given on a fasting stomach and shortly after breakfast. In these comparisons erythromycin stearate was also used in addition to erythromycin propionate and triacetyloleandomycin.

Materials and Methods. Erythromycin propionate was furnished in gelatin capsules by Eli Lilly & Co.; erythromycin stearate was supplied in coated tablets by Abbott Laboratories, and triacetyloleandomycin was provided in capsules by Charles Pfizer & Co. Each of these contained 250 mg. of the respective base equivalent.

In the first study, 10 normal men ranging in weight from 70 to 87 kg. (Av. 76 kg.) were given 2 capsules at 9 A.M. and 9 P.M. daily for 7 days; one-half of them received triacetyloleandomycin and the others erythromycin propionate, 500 mg. base equivalent, in each dose. After a lapse of a week, the procedure was repeated, each subject receiving the alternate drug. On the first, fourth and seventh days, blood was drawn before each of the doses and also at 11 A.M.; the serum was promptly separated and each specimen was placed in 2 rubber stoppered tubes under code numbers and kept frozen in an electric refrigerator at −20° C. until assayed. The serum in one of the tubes was assayed in this laboratory for antistreptococcal and antistaphylococcal activity by a 2-fold dilution method in broth, as in previous studies. The other set of tubes was delivered in the frozen state to the Lilly Laboratories where the serums were assayed by the agar cup-plate diffusion method with *Sarcina lutea* through the courtesy of Dr. R. S. Griffith.

In the second study, comparisons were made of the levels of antibacterial activity in serum following single oral doses of 500 mg. of erythromycin propionate, erythromycin stearate and triacetyloleandomycin. Each of 12 normal men, ranging in weight from 70 to 86 kg. (av. 75 kg.), received 2 of these 3 drugs, each one before and after breakfast at intervals of 6 to 8 days according to a plan shown in Table 1. Bloods were drawn before each dose and again 1, 2, 4, 12 and 25 hours later. Breakfast was taken either after the 2-hour blood was drawn or within one-half hour after the dose. The

serums were assayed in the same manner as above.

The susceptibility of the test strains to the various antibiotics used in this study are shown in Table 2. In the cup-plate method, oleandomycin base was used as a standard of reference in both studies; erythromycin base was used as the standard for comparison in the first study and erythromycin propionate was used in the second, with the levels expressed in terms of erythromycin base equivalents.

TABLE 1.—PLAN OF STUDY II (SINGLE DOSES)

	Dose Given on Day:			
Subjects	*1*	*8*	*15*	*21*
A, B, C, D	ES_a	ES_p	EP_a	EP_p
E, F, G, H	EP_a	EP_p	TAO_a	TAO_p
I, J, K, L	TAO_a	TAO_p	ES_a	ES_p

Each dose consisted of 2 capsules, 250 mg. each (base equivalent)

EP_a = Erythromycin propionate, before breakfast
EP_p = " , after "
ES_a = " stearate, before "
ES_p = " " , after "
TAO_a = Triacetyloleandomycin, before "
TAO_p = " , after "

Breakfast was taken either after the 2-hour blood was drawn or the dose was given within ½ hour after breakfast.

TABLE 2.—*IN VITRO* SUSCEPTIBILITY OF TEST STRAINS TO THE ANTIBIOTICS USED IN THIS STUDY

	Minimum Inhibiting Concentration mcg. per ml.		
Antibiotic	*Strep. 98*	*Staph. 209 P*	*S. lutea*
Erythromycin base	0.011*	0.16*	0.013
Erythromycin propionate	0.012	0.12	0.010
Erythromycin stearate	0.012	0.14	0.014
Oleandomycin base	0.10*	0.35*	0.083
Triacetyloleandomycin	0.49*	2.6	0.335

*Average of 16 determinations in both parts of the study. Others are average of 7 tests in second part of the study. These tests done by a 2-fold dilution method in brain-heart infusion broth, pH 7.2.

The minimum measured concentration in the agar cup-plate method, employing *S. lutea*, was 0.3 mcg. per ml. of oleandomycin base and 0.03 mcg. per ml. of erythromycin base.

Results. ANTISTREPTOCOCCAL AND ANTISTAPHYLOCOCCAL ACTIVITY OF SERUM OF NORMAL ADULTS DURING ORAL ADMINISTRATION OF 500 MG. ERYTHROMYCIN PROPIONATE AND TRIACETYLOLEANDOMYCIN EVERY 12 HOURS. The average values for the maximum inhibiting dilution of serum that inhibited *Streptococcus* 98 and *Staphylococcus 209P* at each of the intervals studied are shown in Table 3 with their standard deviations and the significance of the differences ("P" values). The average levels are also shown in the upper 2 portions of Fig. 1. These average values were all higher during the administration of erythromycin than when triacetyloleandomycin was given. The

differences in antistreptococcal activity were highly significant at most of the intervals studied, but did not achieve the 95% confidence level in some instances. When *Staph. 209P* was used for the assays, the differences were not statistically significant at most of the intervals.

CONCENTRATIONS OF ANTIBIOTICS IN SERUM DURING REPEATED DOSES. The results of the assays done by the cup-plate method with *S. lutea* as the test organism are summarized in the lowest panel of Fig. 1 and in Table 4. Only the comparisons based on calculations from the erythromycin standard are

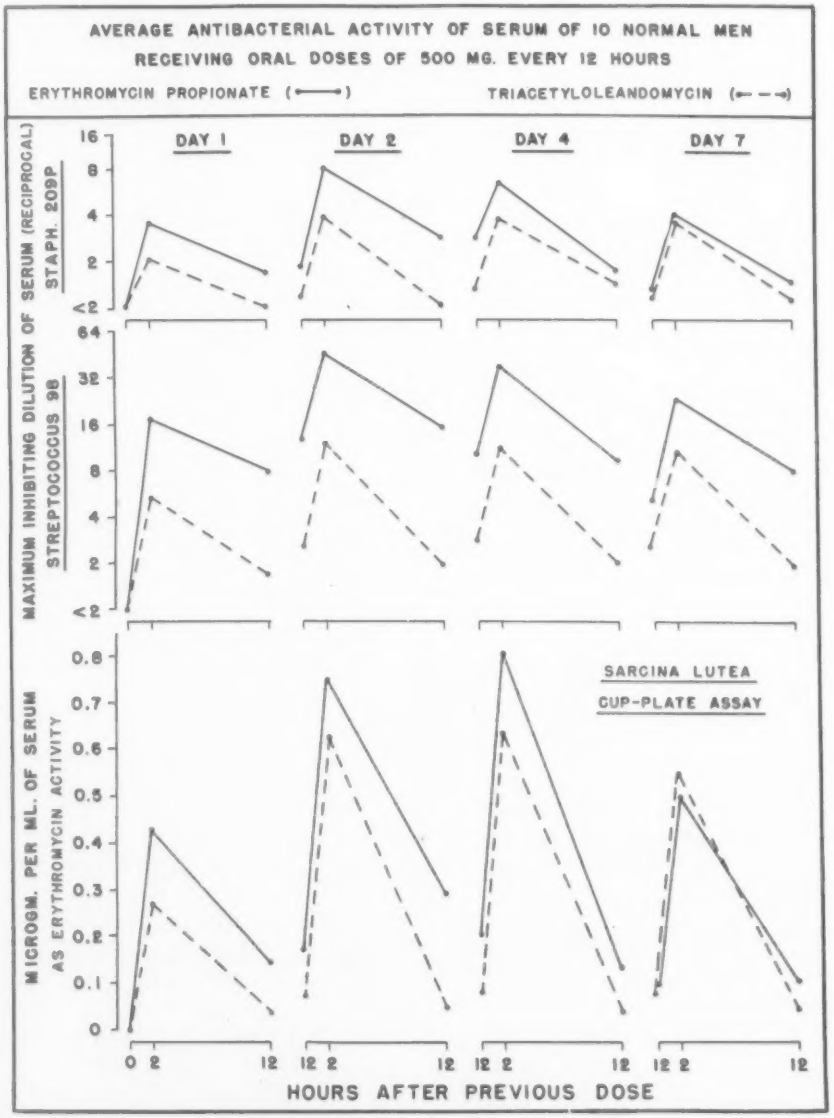


Fig. 1

shown in the figure, but those based on the oleandomycin standard were very similar when the scale was adjusted. The average values expressed as activity of both erythromycin and oleandomycin are listed in Table 4. Here again it is seen that, when they are compared by the same standard, the concentrations of antibiotic were higher during administration of the doses of erythromycin propionate than while the triacetyloleandomycin was given, but the differences were not all statistically significant. On the other hand, when the levels are compared on the basis of the homologous standards, the concentrations of oleandomycin produced by the triacetyloleandomycin were all

TABLE 3.—ANTIBACTERIAL ACTIVITY OF SERUM OF THE SAME 10 NORMAL MEN GIVEN ERYTHROMYCIN PROPIONATE (EP) AND TRIACETYLOLEANDOMYCIN (TAO) ORALLY IN DOSES OF 500 MG. EVERY 12 HOURS FOR 7 DAYS

Day	Hours After Previous Dose*	Maximum Number of Twofold Dilutions of Serum (Average ± SD) that Inhibited: Streptococcus 98 EP	Streptococcus 98 TAO	Streptococcus 98 "P"	Staphylococcus 209P EP	Staphylococcus 209P TAO	Staphylococcus 209P "P"
1	2	4.1 ± 2.6	2.4 ± 1.0	>0.05	1.8 ± 1.6	1.1 ± 0.8	>0.05
	12	3.0 ± 1.0	0.8 ± 0.4	<0.001	0.8 ± 0.9	0.1 ± 0.2	<0.05
2	12	3.7 ± 1.2	1.4 ± 0.5	<0.001	0.9 ± 1.0	0.3 ± 0.4	>0.05
	2	5.5 ± 1.4	3.6 ± 0.4	<0.001	3.0 ± 1.4	2.0 ± 0.3	<0.05
	12	4.0 ± 1.6	1.0 ± 0.5	<0.001	1.5 ± 1.1	0.1 ± 0.2	<0.01
4	12	3.4 ± 1.8	1.5 ± 0.4	<0.01	1.5 ± 1.6	0.4 ± 0.3	>0.05
	2	5.3 ± 1.8	3.5 ± 0.8	<0.02	2.7 ± 2.1	1.9 ± 0.5	>0.05
	12	3.2 ± 1.6	1.0 ± 0.3	<0.001	0.8 ± 1.3	0.5 ± 1.1	>0.05
7	12	2.4 ± 1.3	1.4 ± 0.7	>0.05	0.4 ± 0.7	0.3 ± 0.3	>0.05
	2	4.6 ± 2.1	3.4 ± 1.3	>0.05	2.1 ± 1.5	1.9 ± 0.7	>0.05
	12	3.0 ± 0.8	1.0 ± 0.2	<0.001	0.6 ± 0.8	0.2 ± 0.2	>0.05

*Dose given at 9 A.M. and 9 P.M.; serum samples obtained at 9 A.M., 11 A.M. and 9 P.M. The initial serum obtained before the first dose showed no demonstrable activity in every instance. One week elapsed between the 2 drugs.

TABLE 4.—CONCENTRATIONS OF ANTIBIOTIC ACTIVITY IN SERUM OF SAME 10 NORMAL MEN GIVEN 500 MG. ORAL DOSES OF ERYTHROMYCIN PROPIONATE AND TRIACETYLOLEANDOMYCIN EVERY 12 HOURS FOR 7 DAYS

Day	Hours After Previous Dose*	Concentration of Antibiotic Activity in Serum mcg. per ml. ± SD, expressed as: Erythromycin Activity EP	Erythromycin Activity TAO	Erythromycin Activity "P"	Oleandomycin Activity EP	Oleandomycin Activity TAO	Oleandomycin Activity "P"
1	2	0.43 ± 0.39	0.27 ± 0.21	>0.05	6.6 ± 5.7	3.4 ± 2.4	>0.05
	12	0.15 ± 0.10	0.03 ± 0.02	<0.01	2.0 ± 1.3	0.4 ± 0.2	<0.01
2	12	0.17 ± 0.13	0.08 ± 0.03	<0.05	2.2 ± 1.5	1.0 ± 0.5	<0.05
	2	0.75 ± 0.89	0.63 ± 0.09	>0.05	8.2 ± 6.7	8.9 ± 3.1	>0.05
	12	0.29 ± 0.22	0.05 ± 0.01	<0.01	3.7 ± 2.6	0.6 ± 0.2	<0.01
4	12	0.20 ± 0.26	0.08 ± 0.04	>0.05	3.2 ± 3.8	1.4 ± 0.7	>0.05
	2	0.81 ± 0.66	0.63 ± 0.27	>0.05	11.2 ± 8.0	9.0 ± 4.3	>0.05
	12	0.13 ± 0.08	0.04 ± 0.01	<0.01	2.2 ± 1.1	0.7 ± 0.2	<0.001
7	12	0.09 ± 0.11	0.08 ± 0.05	>0.05	1.5 ± 1.5	1.3 ± 0.8	>0.05
	2	0.50 ± 0.53	0.55 ± 0.36	>0.05	7.1 ± 7.3	8.6 ± 5.0	>0.05
	12	0.10 ± 0.07	0.04 ± 0.04	<0.05	1.8 ± 1.1	0.9 ± 0.6	<0.05

*Doses given at 9 A.M. and 9 P.M.; serum samples obtained at 9 A.M., 11 A.M. and 9 P.M.[5] The initial serum obtained before the first dose showed no demonstrable activity in any instance. One week elapsed between the 2 drugs.

significantly higher than the concentrations of erythromycin obtained at the corresponding intervals when the subjects were taking erythromycin propionate. This reflects the better absorption of triacetyloleandomycin.

ANTIBACTERIAL ACTIVITY OF SERUM AFTER SINGLE DOSES OF 500 MG. (BASE EQUIVALENT) OF ERYTHROMYCIN PROPIONATE, ERYTHROMYCIN STEARATE AND TRIACETYLOLEANDOMYCIN. In the second study, each of 12 normal men took 2 of the 3 test drugs, each before and after breakfast; each of the preparations was thus given before and after the meal to 8 subjects and each subject took 4 doses about a week apart. The control serums obtained before each dose showed no demonstrable activity in any of the tests. The average levels of antistreptococcal and antistaphylococcal activity of the serums after the doses, as determined by the maximum inhibiting dilutions of the serum for those organisms are depicted in Fig. 2. It is seen that, for the doses given in the fasting state, the highest average levels of activity against both test organisms and at all hours were produced by erythromycin propionate and the lowest by triacetyloleandomycin. These differences are similar to those previously demonstrated (Hirsch, Kunin and Finland[14]). Erythromycin stearate yielded intermediate levels that were somewhat lower than those found after erythromycin propionate but much higher than those produced by triacetyloleandomycin.

Comparing the levels of activity produced by each preparation when given after the meal with those resulting from its administration before breakfast, it is seen from Fig. 2 that the latter levels were much lower at all intervals after the doses of both erythromycin propionate and erythromycin stearate, whereas with the doses of triacetyloleandomycin the levels were lower for the post-meal doses during the first 2 hours but essentially similar or even slightly higher levels were obtained at 4, 8 and 12 hours when given after the meal. Thus, absorption appeared to be delayed by taking the meals before each of the 3 preparations; absorption was also markedly decreased by the meal in the case of the 2 erythromycin preparations but not with triacetyloleandomycin. When the levels produced by the 3 drugs after breakfast are compared, erythromycin propionate still produced the highest activity after the second hour against both the streptococcus and the staphylococcus, erythromycin stearate produced nearly the same activity against the streptococcus and this was appreciably higher than that produced by triacetyloleandomycin. On the other hand, the antistaphylococcal activity produced by the latter 2 preparations after the meal were similar and only slightly less than that produced by erythromycin propionate given after breakfast.

The average concentrations of antibiotic activity obtained by the cup-plate method are shown in Fig. 3. In the upper portion of this figure are charted the values derived from comparisons with a standard solution of erythromycin and in the lower portion the same results were calculated as oleandomycin activity. In each instance the differences in the levels obtained with the 3 preparations before breakfast are striking and are similar to those seen in Fig. 2. In Fig. 3 the levels are expressed on an arithmetic scale, whereas in Fig. 2 they are charted in a logarithmic scale. The markedly lower levels of activity produced by both of the erythromycin preparations given after breakfast as compared with those resulting from the premeal doses of the respective prep-

arations are also clearly shown. The delay in achieving the peak levels of activity when each of the 3 drugs was given after the meal is also evident from Fig. 3. When triacetyloleandomycin was given after breakfast, antibiotic activity appeared in the serum, and later. Here again it is seen that the meal produced a delay but not a decrease in the absorption of triacetyloleandomycin whereas it markedly decreased as well as delayed somewhat the absorption of the erythromycin preparations.

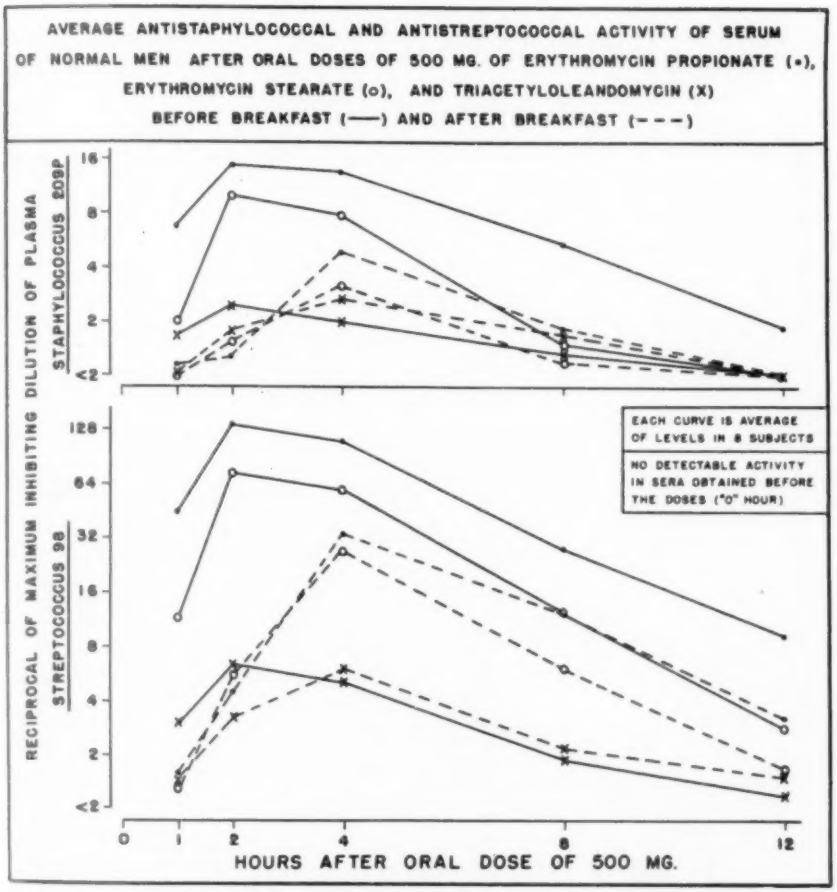


Fig. 2

in higher concentrations than after erythromycin propionate during the first 2 hours, but at 4 hours and later these 2 antibiotics produced essentially the same average activity. Erythromycin stearate given after breakfast produced somewhat lower levels at 4 hours

Comparisons of the peak concentrations and of the "total" activity, as measured by the "area" under the curves of levels in the serum are shown in Table 5. The first 2 columns of numbers in this table give the average peak levels of antistreptococcal and

antistaphylococcal activity expressed as the maximum number of twofold dilutions of serum which inhibit these respective organisms. The average peak concentrations of antibiotic activity expressed as erythromycin and oleandomycin are shown in the third and fourth columns of numbers, respectively. The corresponding values for total activity are listed in the last 4 columns. The standard deviations are shown for each mean value and the significance of differences of these means ("P" values) are given in the lower half of the table.

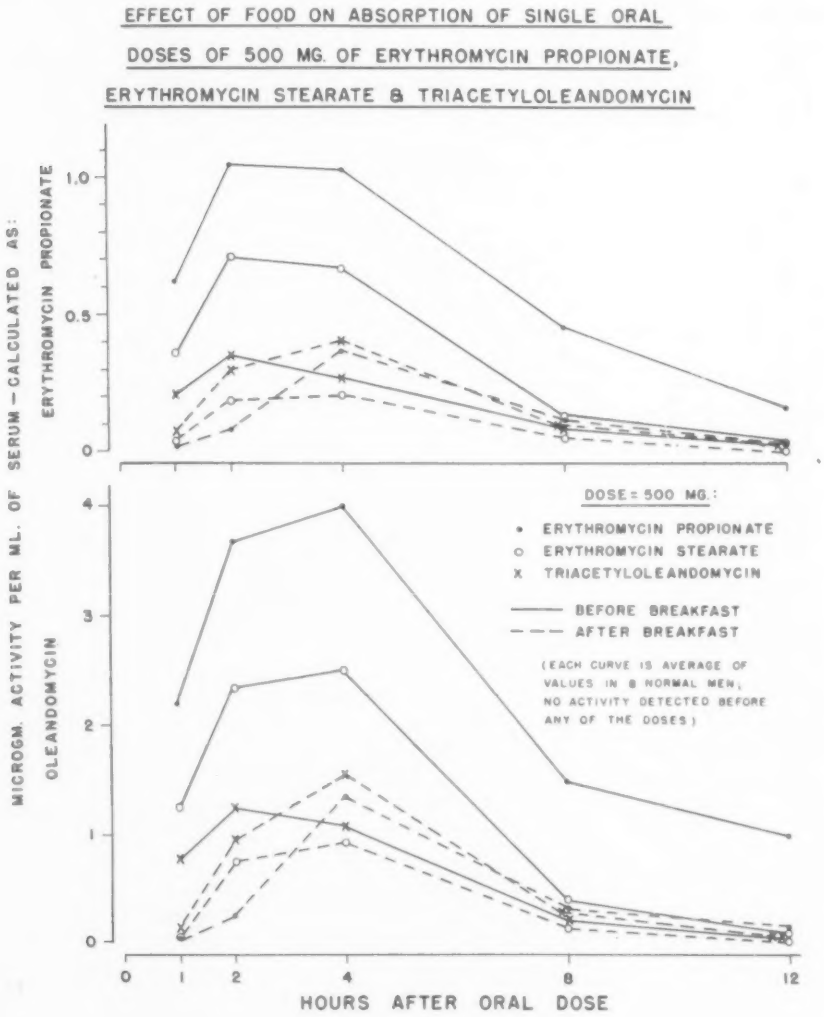


Fig. 3

When the peak concentrations and total activities derived from each of the 3 preparations given before breakfast are compared with the corresponding values for the post-meal doses

TABLE 5.—COMPARISON OF ANTIBACTERIAL ACTIVITY OF SERUM OF NORMAL MEN AFTER SINGLE ORAL DOSES OF 500 MG. OF ERYTHROMYCIN PROPIONATE, ERYTHROMYCIN STEARATE AND TRIACETYLOLEANDOMYCIN, EACH GIVEN BEFORE AND AFTER BREAKFAST

Antibiotic and Relation to Meal§	*Peak Levels of Activity**				*Total Activity (Area) in 25 Hours**			
	Maximum Number of Twofold Dilutions of Serum Which Inhibit		*Mcg. per ml. Activity† in Serum Calculated as:*		*Dilution-Hours of Activity Against*		*Mcg.-Hours Activity Calculated as:*	
	Strep. 98	*Staph. 209P*	*Erythromycin*	*Oleandomycin*	*Strep. 98*	*Staph. 209P*	*Erythromycin*	*Oleandomycin*
EP_a	7.5 ± 0.8	4.2 ± 0.8	1.3 ± 0.6	5.0 ± 2.5	86.4 ± 26.7	37.4 ± 16.3	8.7 ± 5.1	29.8 ± 18.7
EP_p	5.2 ± 0.8	2.3 ± 0.6	0.4 ± 0.1	1.4 ± 0.5	47.2 ± 12.2	11.1 ± 4.9	2.0 ± 0.8	6.9 ± 2.8
ES_a	6.3 ± 0.7	3.5 ± 0.5	0.8 ± 0.3	2.8 ± 0.7	56.9 ± 14.7	17.1 ± 5.0	3.8 ± 1.1	14.3 ± 4.9
ES_p	5.2 ± 0.9	1.9 ± 1.0	0.3 ± 0.1	1.3 ± 0.8	34.7 ± 9.4	6.8 ± 3.9	1.3 ± 0.5	4.7 ± 2.1
TAO_a	2.6 ± 1.1	1.4 ± 0.7	0.4 ± 0.2	1.6 ± 1.0	18.3 ± 8.9	7.0 ± 4.2	1.9 ± 0.8	7.4 ± 4.5
TAO_p	2.9 ± 0.4	1.4 ± 0.2	0.5 ± 0.2	1.8 ± 0.2	21.5 ± 5.5	7.7 ± 2.0	2.9 ± 0.9	8.0 ± 1.8

*Each value is average in 8 subjects ±SD

†Cup-plate agar diffusion method using *S. lutea* as assay organism.

§EP = erythromycin propionate.
ES = erythromycin stearate.
TAO = triacetyloleandomycin.
a = before breakfast
p = after breakfast

Differences	*"P" Values*							
$EP_a - EP_p$	<0.001	<0.001	<0.001	<0.01	<0.01	<0.001	<0.01	<0.01
$ES_a - ES_p$	<0.02	<0.001	<0.02	<0.01	<0.01	<0.001	<0.001	<0.001
$TAO_p - TAO_a$	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
$ES_a - ES_a$	<0.01	>0.05	<0.05	<0.05	<0.02	<0.01	<0.02	<0.05
$EP_a - TAO_a$	<0.001	<0.001	<0.001	<0.01	<0.001	<0.001	<0.01	<0.01
$ES_a - TAO_a$	<0.001	<0.001	<0.01	<0.02	<0.001	<0.001	<0.01	<0.02
$EP_a - ES_p$	<0.001	<0.001	<0.01	<0.01	<0.001	<0.001	<0.01	<0.01
$EP_a - TAO_p$	<0.001	<0.001	<0.01	<0.01	<0.001	<0.001	<0.01	<0.01
$ES_a - TAO_p$	<0.001	<0.001	>0.05	<0.02	<0.001	<0.001	>0.05	<0.01
$EP_p - ES_p$	>0.05	>0.05	>0.05	>0.05	<0.05	>0.05	<0.05	>0.05
$EP_p - TAO_p$	<0.001	<0.001	>0.05	>0.05	<0.001	>0.05	>0.005	>0.05
$TAO_p - ES_p$	<0.001‡	>0.05	>0.05	<0.05	<0.01‡	>0.05	<0.001	<0.01

‡These values, obtained with Strep. 98, are the only ones for which $ES_p > TAO_p$; for all other values listed $TAO_p > ES_p$. Note also that average values listed for TAO_p are all greater than the corresponding ones of TAO_a.

of the same drugs, the differences are highly significant in the case of erythromycin propionate and erythromycin stearate. The mean values obtained with triacetyloleandomycin after breakfast were the same or slightly higher than those achieved when this drug was given before breakfast, but the differences were not significant.

When given before breakfast, each of the erythromycin preparations produced significantly higher peak levels and total activity than did triacetyloleandomycin. The differences in the average peak levels of erythromycin propionate and stearate were not significant, but the total activities produced by the former were significantly greater than those of the latter in each instance.

The peak levels and total activity produced in the serum by erythromycin propionate when given before breakfast were considerably greater than the corresponding values for either erythromycin stearate or triacetyloleandomycin given after the meal and the differences were highly significant in every instance. Erythromycin stearate given before the meal also produced higher peak levels and total activity when compared with triacetyloleandomycin given after breakfast; the differences were statistically significant except when expressed as erythromycin activity.

Finally, when the average peak levels and total activities produced by the 3 preparations given after the meals are compared, the differences were, for the most part, not significant except that the antistreptococcal activity of each of the erythromycin preparations was significantly greater than that derived from triacetyloleandomycin.

The comparisons thus far have been made on the basis of the activity of the serum as measured by the same standard, and each of 4 standards of comparison were used, namely antistreptococcal and antistaphylococcal activity and activity expressed as erythromycin or as oleandomycin. By each of these standards, erythromycin propionate and erythromycin stearate given before breakfast produced significantly higher levels and total antibacterial activity than triacetyloleandomycin whether given before or after the meal. Erythromycin propionate produced greater activity than the stearate when each was given after a meal, but most of the differences in the activity of the 3 drugs given after the meal were not significant, although this varied with the different assay organisms.

COMPARISONS BASED ON CONCENTRATIONS OF HOMOLOGOUS ANTIBIOTIC. In the usual investigations of any single antibiotic its absorption is generally measured by the concentrations produced in the blood; these are calculated by comparison with a standard solution of the same antibiotic. Since antibiotics vary markedly in their antibacterial activity against different test organisms, as seen in Table 2 for the ones under study here, comparisons of the activity of different antibiotics on the basis of concentrations of the homologous antibiotic in the serum may be grossly deceptive.

To illustrate this, the average concentrations of the homologous antibiotics resulting in the serum from ingestion of the single doses of the 3 preparations under study are shown in Fig. 4. From this figure it is seen that, on a weight basis, the premeal doses of triacetyloleandomycin and erythromycin propionate were absorbed about equally well; the former produce a somewhat higher peak level that was attained sooner, and the latter maintained higher concentrations after 4 hours. Erythromycin stearate given before breakfast

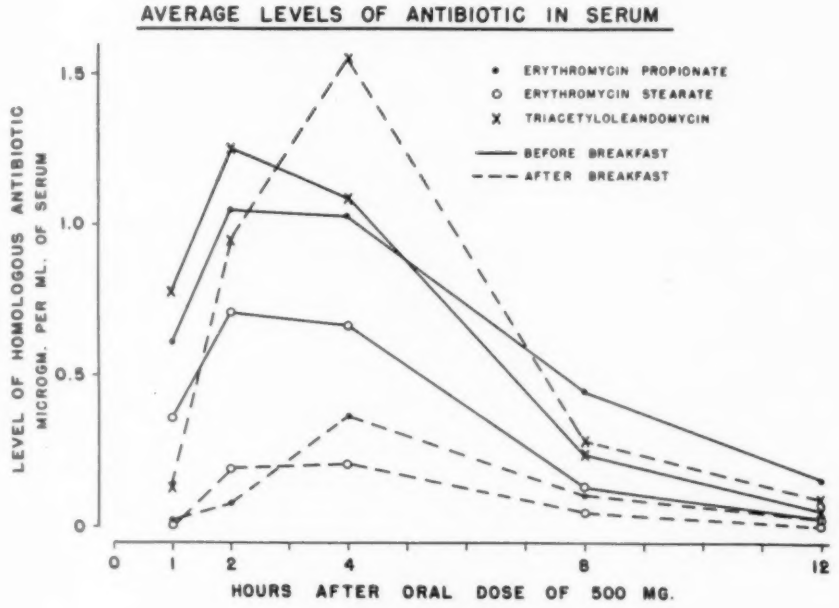


Fig. 4

TABLE 6.—COMPARISONS OF PEAK CONCENTRATIONS AND TOTAL ACTIVITY PRODUCED IN SERUM BY EACH ANTIBIOTIC—CALCULATED IN TERMS OF THE HOMOLOGOUS STANDARD*

Antibiotic	*Average Peak Concentration Mcg. per ml.*	*Average Total Activity (Area) Mcg.-Hrs. ± SD*
Erythromycin propionate		
Before breakfast (EP_a)	1.3 ± 0.6	8.7 ± 5.1
After breakfast (EP_p)	0.4 ± 0.1	2.0 ± 0.8
Erythromycin stearate		
Before breakfast (ES_a)	0.8 ± 0.3	3.8 ± 1.1
After breakfast (ES_p)	0.3 ± 0.1	1.3 ± 0.5
Triacetyloleandomycin		
Before breakfast (TAO_a)	1.6 ± 1.0	7.4 ± 4.5
After breakfast (TAO_p)	1.8 ± 0.2	8.0 ± 1.8
	"P" Values	
Differences		
EP_a TAO_a	>0.05	>0.05
TAO_p—EP_p	<0.001	<0.001
TAO_a—ES_a	>0.05	<0.05
TAO_p—ES_p	<0.001	<0.001
EP_a —TAO_p	>0.05	>0.05
TAO_p—ES_a	<0.01	<0.001

*Erythromycin propionate (concentrations expressed in base equivalents) and oleandomycin base were used as standards for these comparisons. The doses were given either 2 hours before breakfast or within ½ hour after breakfast.

yielded levels of erythromycin that were lower than those produced by erythromycin propionate taken before the meal. The absorption of the doses given after the meal was slower in every instance, the average peak concentration of oleandomycin being achieved 4 hours after the dose of triacetyloleandomycin; this was higher than the peak level produced by the same dose given on a fasting stomach. The levels of erythromycin produced by the propionate and the stearate after breakfast were much lower, although in terms of activity they were similar, as seen in Fig. 3 and in Table 5.

The average peak concentrations and total activity produced by the single doses of 500 mg. of the 3 preparations under study are listed in terms of the homologous antibiotic in Table 6. These data reflect the relative absorption of the different preparations and the effects of the meal, but they do not reflect the relative activity of the erythromycin preparations as compared with that of triacetyloleandomycin. The only significant differences in absorption were demonstrated when the doses were given after breakfast; triacetyloleandomycin given after the meal was significantly better absorbed than either of the erythromycin preparations given in this manner (TAO_p–EP_p and TAO_p–ES_p) and also better than erythromycin stearate given before the meal (TAO_p–ES_a). However, there was no significant difference between the absorption of triacetyloleandomycin given either before or after a meal and erythromycin propionate taken on a fasting stomach (EP_a–TAO_a and EP_a–TAO_p)

Discussion. It is of interest to review the background of the present study and the previous reports dealing with similar studies. The antibacterial activity of erythromycin has been shown to be decreased markedly and progressively with increasing acidity of the medium (Haight and Finland[12]). This may account, in large part, for the irregular absorption of erythromycin after its oral administration in norman individuals (Griffith[9], Haight and Finland[12], Heilman *et al.*[13], Josselyn, Endicott and Sylvester[17,18,31], Kirby, Maple and O'Leary[20], Smith, Dyke and Griffith[29]) and for the better and more regular absorption in patients with pernicious anemia lacking free acid in their gastric juice (Smith, Dyke and Griffith[29]).

Attempts have been made to increase the absorption of erythromycin by protecting it from the acid gastric juice. Tablets coated with an acid-resistant, alkali soluble substance were found to yield more regular and better absorption of erythromycin base (Griffith[9], Josselyn and Sylvester[18], Kirby, Maple and O'Leary[20], Perry, Hall and Kirby[25]), so that the levels obtained in normal individuals with coated tablets were similar to those produced in patients with pernicious anemia (Smith, Dyke and Griffith[29]). Heavier enteric coating resulted in delayed absorption (Josselyn, Endicott and Sylvester[17]). Absorption of erythromycin base has also been shown to be reduced markedly if taken with a meal, either in a plain tablet or in a gelatin capsule (Josselyn and Sylvester[18]). It was reported that absorption of erythromycin given in the suitable coated tablet was unaffected by a meal, except for a slight delay, and also was more regular if given before a meal (Josselyn and Sylvester[18]). Administration of the base with alkali had variable effects; sodium citrate did not improve absorption, whereas administration together with aluminum hydroxide gel resulted in higher levels both before and after meals, but the food nevertheless depressed the absorption (Josselyn and Sylvester[18]).

Attempts have also been made to improve the absorption of erythromycin and also to make it more palatable by the preparation of salts and esters (Clark and Freifelder[4], Clark and Varner[5], Josselyn, Endicott and Sylvester[17], Murphy[24], Stephens and Conine[30], Taylor and Howes[32]). Thus, erythromycin ethyl carbonate was found to be nearly tasteless and its absorption not affected by food (Murphy[24]). Erythromycin stearate in the form of tablets or as an aqueous suspension also produced better levels; this was found to be absorbed as well as the base in the acid resistant tablet and not affected by gastric secretions (Josselyn, Endicott and Sylvester[17,31]).

More recently, monopropionyl erythromycin was prepared (Stephens and Conine[30]); this ester was shown to be absorbed faster and to produce higher and more persistent levels in the serum as compared with erythromycin base given in capsules or as tablets coated with an acid-resistant substance (Griffith[8], Griffith *et al.*[10], Stephen and Conine[30]). The propionate was found to have the same activity as the base and the higher levels from oral administration of the former were considered to be related, at least in part, to its lesser excretion in the bile (Griffith *et al.*[10], Lee *et al.*[22]). Cross-over studies in healthy subjects with doses given 2 hours before breakfast, showed that erythromycin proprionate produced more than 100% higher levels of antistreptococcal activity in the serum than erythromycin base in coated tablets (Perry, Hall and Kirby[25]). After oral administration of erythromycin propionate, both erythromycin propionate and erythromycin base are found in the blood and the urine in rats whereas only the base is found in dogs (Lee *et al.*[22]). In man, however, about 80% of the propionate is recovered unchanged in the urine after oral administration (Griffith *et al.*[10]).

Oleandomycin, usually tested as the phosphate or hydrochloride, is much less active *in vitro* than erythromycin against most strains of streptococci and sensitive staphylococci (Andrieu *et al*[1], Garrod[7], Jones and Finland[15,16], Petersdorf, Curtin and Bennett[26]). Like erythromycin, its antibacterial activity is markedly reduced by increased acidity of the medium (Andrieu *et al.*[1]). Oral doses of oleandomycin produce much lower levels of antistreptococcal and antistaphylococcal activity in serum of normal men than similar amounts of erythromycin (Jones and Finland[16]). Oleandomycin is excreted to a much greater extent in bile and urine than is erythromycin (Kazenko *et al.*[19]).

Various modifications of the oleandomycin structure have been accomplished which do not destroy its antibiotic activity (Celmer, Els and Murai[3]). One of these, triacetyloleandomycin, in which all of the free hydroxyl groups are acetylated, was isolated in crystalline form. This was found to be insoluble in distilled water and in buffered aqueous solution pH 4 to 7, and also lacked the bitter taste of more soluble derivatives. It is also more stable, less hygroscopic and produces higher levels in blood after oral administration as compared with the base, but *in vitro* it was found to be only one-fourth as active as oleandomycin against *Staph. aureaus* and two-fifths as active against S. *lutea* (Celmer[2]). Triacetyloleandomycin is excreted largely as oleandomycin and as the 3-monoacetyl derivative, but other excretory derivatives have also been found (Celmer[2]).

In crossover studies after oral administration of similar doses of triacetyloleandomycin and oleandomycin in normal subjects, much higher levels of antibiotic were produced in the serum (Mellman, Barness and Foltz[23], Shubin, Dumas and Sokmensuer[28])

they were sustained better (Shubin, Dumas and Sokmensuer[28]) and about twice as much antibiotic was recovered with triacetyloleandomycin (Mellman, Barness and Foltz[23]). Triacetyloleandomycin was also said to produce higher levels in the serum than erythromycin (commercial, coated tablets), but this comparison is based on data obtained with erythromycin in another laboratory and at a different time in different subjects in the same laboratory (Shubin, Dumas and Sokmensuer[28]). Triacetyloleandomycin is also reported to be effective in infections of mice with staphylococci resistant to other antibiotics and to produce biological activity (measured in terms of concentrations of the homologous antibiotic) greater than erythromycin and penicillin V (English and McBride[6]). This comparison, however, did not take into account the much greater activity, weight for weight, of the latter antibiotics; for example one strain was 50 times more sensitive to penicillin V than to oleandomycin (Kunin, Pryles and Finland[21]).

In another crossover study serums were obtained 2 hours after the last of 4 doses of 500 mg. of triacetyloleandomycin in capsules and of erythromycin in coated tablets; the serums were assayed for the concentration of the corresponding antibiotic with *S. lutea* in a cup-plate method and for antistaphylococcal inhibition and bactericidal action by a tube dilution method. In this study, the average concentrations of the respective antibiotics were essentially the same, and there was no significant difference between the antistaphylococcal activity in the serums produced by the 2 drugs (Reisch *et al.*[27]).

In this laboratory, similar levels of antistreptococcal and antistaphylococcal activity were found in the serum of normal subjects by the same single oral doses of capsules of triacetyloleandomycin and coated tablets of erythromycin base given ½ to 1 hour before breakfast and also during administration of comparable doses of a suspension of the former and of erythromycin ethyl carbonate every 8 hours for a week (Kunin, Pryles and Finland[21]). However, when single oral doses of capsules of 500 mg. of erythromycin propionate and of triacetyloleandomycin were given to the same normal subjects 2 hours before breakfast, the former produced much higher levels of activity in the serum when tested in a tube dilution method against streptococcus and staphylococcus or when calculated as activity of erythromycin or oleandomycin by comparison with standard solutions of these antibiotics in an agar cup-plate diffusion method using *S. lutea* as the test organism (Hirsch, Kunin and Finland[14]).

In the present study it was shown that, when erythromycin propionate and triacetyloleandomycin were given in repeated doses to the same normal individuals, much of the previously demonstrated great advantage of erythromycin propionate appeared to be lost. Since these doses were taken soon after meals, an attempt was made to determine the effect of a meal on the absorption of these agents and, since it has been shown that the absorption of erythromycin stearate was not affected by a meal (Josselyn and Sylvester[18]), this derivative was also included. The results of this comparison indicated that the absorption of all 3 of these preparations was delayed by a meal; however, whereas the absorption of erythromycin propionate and erythromycin stearate was markedly depressed by the meal, that of triacetyloleandomycin was not similarly affected. Both of the erythromycin preparations given before breakfast produced much greater antibiotic ac-

tivity than triacetyloleandomycin given either before or after breakfast. When the erythromycin preparations were given after breakfast the resulting activity in the serum was more nearly equal to that produced by triacetyloleandomycin, but some differences were noted, depending on the test organism. Thus, the antistreptococcal activity produced by the erythromycin preparations was significantly greater than that resulting from triacetyloleandomycin, but when measured by the cup-plate method, the activity of the latter was similar to that produced by erythromycin propionate and greater than that produced by erythromycin stearate. The greatest antibacterial effect from oral use of these drugs is therefore obtained by taking the erythromycin derivatives on an empty stomach and delaying the taking of food for about 2 hours after the doses.

It was also shown that real differences in activity may be completely obscured when preparations of different antibiotics are compared on the basis of measurement of concentrations of the homologous antibiotics in the blood. Such comparisons do reveal differences in absorption into the blood stream but do not take into account the variation in antibacterial activity of the different antibiotics, and the variations that can result from differences in the susceptibility of different organisms to the antibiotics under study, their diffusion through agar in the cup-plate method, their binding to serum, and so forth. These factors are included when the same standard of reference is used in comparing the different antibiotics, whether by dilution methods in broth using the same test organisms, or by the agar diffusion methods and calculating from the same standard solution of one or another of the antibiotics.

Summary and Conclusions. Triacetyloleandomycin and erythromycin propionate given in doses of 500 mg. every 12 hours to the same normal adults produced essentially similar antistreptococcal and antistaphylococcal activity in the serum, as measured by a tube-dilution test and similar concentrations of antibiotic when determined by the cup-plate method with *S. lutea* and expressed either as erythromycin or as oleandomycin.

Absorption of erythromycin propionate and erythromycin stearate was markedly depressed by a meal, whereas that of triacetyloleandomycin was not. A dose of 500 mg. of erythromycin propionate or stearate given before breakfast produced much greater activity in serum than a similar dose (all as base equivalents) of triacetyloleandomycin given either before or after breakfast as measured by any of the 4 methods noted above. When they were given after a meal all 3 preparations produced more nearly similar activity. On a weight basis, erythromycin propionate given before breakfast was absorbed as well as triacetyloleandomycin given either before or after the meal, but erythromycin stearate was less well absorbed at either time, as was also erythromycin propionate when given before breakfast.

The importance of comparing different antibiotics on the basis of the same standard of reference was emphasized.

REFERENCES

1. **Andrieu, G., Monnier, J., Quercy, J., and Bourse, R.:** Presse Méd., **65**, 865, 1957.
2. **Celmer, W. D.:** Antibiotics Annual, p. 277, 1958–1959.
3. **Celmer, W. D., Els, H., and Murai, K.:** Ibid., p. 476, 1957–1958.

4. **Clark, R. K., Jr.,** and **Freifelder, M.:** Antibiot. & Chemother., **7**, 483, 1957.
5. **Clark, R. K., Jr.,** and **Varner, E. L.:** Ibid., **7**, 487, 1957.
6. **English, A. R.,** and **McBride, T. J.:** Ibid., **8**, 424, 1958.
7. **Garrod, L. P.:** Brit. Med. J., **2**, 57, 1957.
8. **Griffith, R. S.:** Antibiotics Annual, p. 364, 1958–1959.
9. Idem.: Ibid., pp. 269–278, 1954–1955.
10. **Griffith, R. S., Stephens, V. C., Wolfe, R. N., Borneci, W. S.,** and **Lee, C-C:** Antibiot. Med. & Clin. Ther., **5**, 609, 1958.
11. **Grove, D. C.,** and **Randall, W. A.:** Assay Methods of Antibiotics: A Laboratory Manual. New York: Medical Encyclopedia, Chap. 10, Erythromycin, pp. 96–103, 1955.
12. **Haight, T. H.,** and **Finland, M.:** Proc. Soc. Exper. Biol. & Med., **81**, 175, 1952.
13. **Heilman, F. R., Herrell, W. E., Wellman, W. E.,** and **Geraci, J. E.:** Proc. Staff Meet., Mayo Clin., **27**, 285, 1952.
14. **Hirsch, H. A., Kunin, C. M.,** and **Finland, M.:** New England J. Med., **260**, 408, 1959.
15. **Jones, W. F., Jr.,** and **Finland, M.:** Am. J. Clin. Path., **27**, 528, 1957.
16. Iidem: New England J. Med., **257**, 481, 1957.
17. **Josselyn, L. E., Endicott, C.,** and **Sylvester, J. C.:** Antibiotics Annual, pp. 279–282, 1954–1955.
18. **Josselyn, L. E.,** and **Sylvester, J. C.:** Antibiot. & Chemother., **3**, 63, 1953.
19. **Kazenko, A., Sorenson, O. J., Jr., Wolf, L. M., Dill, W. A., Galbraith, M.,** and **Glazko, A. J.:** Ibid., **7**, 410, 1957.
20. **Kirby, W. M. M., Maple, F. M.,** and **O'Leary, B.:** Ibid., **3**, 473, 1953.
21. **Kunin, C. M., Pryles, C. V.,** and **Finland, M.:** Pediatrics, **22**, 422, 1958.
22. **Lee, C-C, Anderson, R. C., Henderson, F. G., Worth, H. M.,** and **Harris, P. N.:** Antibiotics Annual, p. 354, 1958–1959.
23. **Mellman, W. J., Barness, L. A.,** and **Foltz, E. L.:** Ibid. p. 319, 1958–1959.
24. **Murphy, H. W.:** Ibid., p. 500, 1953–1954.
25. **Perry, D. M., Hall, G. A.,** and **Kirby, W. M. M.:** Ibid., p. 375, 1958–1959.
26. **Petersdorf, R. G., Curtin, J. A.,** and **Bennett, I. L., Jr.:** A.M.A. Arch. Int. Med., **100**, 927, 1957.
27. **Reisch, A. J., Martin, W. J., Nichols, D. R.,** and **Heilman, F. R.:** Proc. Staff Meet., Mayo Clin., **33**, 187, 1958.
28. **Shubin, H., Dumas, K.,** and **Sokmensuer, A.:** Antibiotics Annual, pp. 679–684, 1957–1958.
29. **Smith, J. W., Dyke, R. W.,** and **Griffith, R. S.:** J. Am. Med. Assn., **151**, 805, 1953.
30. **Stephens, V. C.,** and **Conine, J. W.:** Antibiotics Annual, p. 346, 1958–1959.
31. **Sylvester, J. C.,** and **Josselyn, L. E.:** Antibiot. & Chemother., **3**, 930, 1953.
32. **Taylor, R. M.,** and **Howes, B. G.:** Fed. Proc., **13**, 410, 1954.

SUMMARIO IN INTERLINGUA

Le Effecto De Alimentos Super Le Absorption De Propionato E Stearato De Erythromycina E Triacetyloleandomycina

Triacetyloleandomycina e propionato de erythromycina, administrate in doses de 500 mg omne 12 horas al mesme adultos normal, produceva essentialmente le mesme activitate antistreptococcal e antistaphylococcal in le sero (mesurate per le test a dilution in tubos) e le mesme concentration de antibiotico (determinate per le test anular con *Sarcina lutea* e exprimite como erythromycina o como oleandomycina).

Le absorption de propionato e de stearato de erythromycina esseva deprimite marcatemente per le ingestion de un repasto. Nulle tal effecto esseva notate in le caso de triacetyloleandomycina. Un dose de 500 mg de propionato o de starato de erythromycina administrate ante le prime repasto del die produceva multo plus alte grados de activitate in le sero que un simile dose (omnes como equivalentes basic) de triacetyloleandomycina administrate ante o post le prime

repasto del die (e mesurate secundo non importa le qual de 4 methodos identificate in le texto). Quando le 3 agentes esseva administrate post un repasto, lor activitates respective esseva plus simile le unes al alteres. Calculate pro equal pesos, propionato de erythromycina administrate ante le prime repasto del die esseva absorbite tanto ben como triacetyloleandomycina administrate ante o post ille repasto. Del altere latere, stearato de erythromycina esseva absorbite minus ben, tanto in administrationes ante como etiam post le prime repasto, e le mesmo valeva pro propionato de erythromycina in administrationes antejentacular.

Es sublineate le importantia de comparar differente antibioticos super le base del mesme standard de referentia.

SUMMARIO IN INTERLINGUA

(See page 754 for original article)

Correlation Inter Le Habitude Del Fumar E (1) Le Presentia De Streptococcos Hemolytic E (2) Le Titros De Antistreptolysina O

Esseva investigate le relation possibile inter le habitude del fumar in adultos e le frequentia del constatation de streptococcos hemolytic beta in culturas de tamponage gurgital. Le analyse del datos in 1.812 tamponationes gurgital monstrava que streptococcos beta esseva isolate ab le gurgites de fumatores presente duo vices plus frequentemente que ab gurgites de non-fumatores o fumatores passate. Le differentia esseva statisticamente multo significative ($p<0{,}001$). Organismos de gruppo A esseva isolate etiam plus frequentemente ab le gurgites del fumatores, sed in iste caso le differentia esseva minus frappante ($p<0{,}05>0{,}02$).

Studios de antistreptolysina O (1.611 specimens) revelava nulle appreciabile differentia inter le seros de fumatores e non-fumatores.

Le augmentate frequentia de isolation streptococcal in fumatores in comparation con non-fumatores o fumatores passate es possibilemente le effecto de un influentia exercite per constituentes del fumo super le streptococcos o de un influentia exercite per tal constituentes super le barriera del membrana mucose in le hospite.

EFFECTS OF CERTAIN PURE LONG CHAIN POLYUNSATURATED FATTY ACID ESTERS ON THE BLOOD LIPIDS OF MAN

PRELIMINARY STUDIES ON THE USE OF POLYUNSATURATED FATTY ACIDS IN ATHEROSCLEROSIS

By Howard E. Worne, Ph.D., D.Sc.

AND

Lawrence W. Smith, M.D.

(From the Departments of Experimental Medicine and Biologic Chemistry and Nutrition, National Foundation for Metabolic Research, Erlton, New Jersey)

The role of the polyunsaturated fatty acids in human metabolism is a constantly expanding study resulting from the interest created by the observation that abnormal concentrations of cholesterol, neutral fats and other blood lipids are possibly involved in the pathogenesis of arteriosclerosis and associated coronary disease. While little is known as to the exact biochemical pathways followed by the essential unsaturated fatty acids in mammalian metabolism, preliminary data has demonstrated that they are chemical compounds of the greatest importance.

It is the purpose of this paper to determine the cholesterol depressant effect of relatively pure ethyl linoleate, ethyl linolenate, methyl arachidonate, methyl clupanodonate and methyl docosahexaenoate individually and a mixture of these essential polyunsaturated fatty acids in the form of alkyl esters.

The biochemical activity of the dienoic and trienoic members of the polyethenoid acids apparently depends upon having double bonds at the 9:10 and 12:13 carbons, but not on the terminal group which may be a carboxyl, hydroxyl or ester group (Turpeinen[50]).

Although the exact positions of the double bonds in arachidonic acid, clupanodonic acid and docosahexaenoic acid, 4, 5, and 6 double bonds respectively, have been tentatively established, little is known about the exact locations of the double bonds in the molecular structure necessary to confer essential function. It is known, however, that conjugation of the double bonds alters the biostatics of the acids and completely destroys their original biological activity. It has been observed that the polyunsaturated fatty acids are deposited in the tissues primarily as phospholipids which may serve to protect them from oxidation in the mitochondria, in which oxidation of the free unsaturated fatty acids is known to occur (Rieckehoff, Holman and Burr[43]).

The polyunsaturated fatty acids vary as to their biological activity. Linoleic acid, arachidonic acid and docosahexaenoic acid, in ascending order, exhibit the greatest efficiency per weight basis in growth promotion, stimulation of lactation and elimination of induced skin lesions. Linolenic acid and clupanodonic acid are of greatly reduced biological activity (Greenberg *et al.*[22], Hume *et al.*[30]). A combination of linoleic acid and linolenic acid, however, exhibits a synergism which results in

equal bio-potency (Deuel, Martin and Alfin-Slater[16]). A greatly enhanced effectiveness is observed when arachidonic acid and docosahexaenoic acid are fed in combination with linoleic acid. When 5 mg. each of linoleic acid and arachidonic acid were fed, the mixture was found to have a biological activity equivalency equal to 32 mg. of linoleic acid (Greenberg *et al.*[21]). Whether this difference is to be attributed to a synergism of arachidonate or linoleate activity, or *vice versa*, cannot be answered at this juncture. Using linoleic acid as a standard of 1 arachidonic acid has a biological activity of 3.5 while docosahexaenoic acid has an activity ratio of 5 when fed to fat deficient animals. When arachidonic acid and linoleic acid were fed as a mixture, the biological activity ratio was 6.2:1 (Greenberg *et al.*[22]).

In order to understand the role of the polyunsaturated fatty acids in the biochemistry of disease, it is first necessary to determine the results of induced deficiency in the mammalian metabolism. Numerous investigators have determined that animals maintained on diets deficient in the essential unsaturated fatty acids exhibit rather divergent striking abnormalities (Burr and Burr[12,13], Hansen, Holmes and Wiese[26], Hansen, Sinclair and Wiese[27], Smedley-Maclean and Nunn[48]). Growth was very much retarded and in addition, the animals matured very slowly (Reid[42]). Although the specific function is uncertain, it has been concluded that essential fatty acids have a key position in the formation and development of new cells (Decker, Fillerup and Mead[15]). In several of the species studied, degeneration of the kidneys occurred as evidenced by hematuria and kidney lesions. Macroscopically the organs were pale and enlarged with finely pitted and coarse granular surfaces. Although the pathogenesis of the renal lesions is not clear, the principle area of damage is in the tubular epithelium (Aaes-Jørgensen and Dam[1]). Histologic studies have shown considerable calcification of the renal tubules and necrotic areas in the renal medulla (Borland and Jackson[10]). Detailed studies on the internal organs of both male and female animals have shown the profound effects of essential fatty acid deficiency (Panos and Finerty[37,38]).

Necropsy findings revealed relatively heavy livers, hearts and kidneys with intertubular accumulation of blood in the kidney and fatty accumulations in the hepatic veins. The effects of induced deficiency on the endocrine system is of major importance. Atrophic thyroids in both sexes, hyperplasia of the adrenals, genital degeneration in the males and irregular estrous cycles in the females, which, coupled with pituitary dysfunctions, evidenced by excessive water consumption, high respiratory quotients and high metabolic rates, signifies the magnitude of the interrelationship between the endocrines and the essential fatty acids. Histologic examinations indicate that deficiency caused underdevelopment of the uterine mucosa and corpora lutea with the result that embryonic resorption was observed or prolonged *in utero* retention (Maeder[33]). In the male animal there was an atrophy of the testes, degeneration of the tubular epithelium, absence of sperm and the appearance of giant cells. The seminal vesicles were small and flaccid and the prostrate was atrophic (Evans, Lepkovsky and Murphy[18]). One of us (HEW) reported that dogs maintained on a diet deficient in the essential unsaturated fatty acids evidenced reduced secretion of the urinary 17-ketosteroids and that return to normal levels was determined after the addition of the essential fatty acids to the diet

(Worne[54]). Of particular interest to the present study is the finding that cholesterol synthesis by liver homogenates is inhibited by the presence of linoleic acid (Wood and Migicovsky[53]).

Dogs maintained on diets deficient in the essential fatty acids had a higher ratio of cholesterol synthesis in the skin than control animals maintained on a normal diet (Hansen and Wiese[28]). Previous research has demonstrated that a high percentage of the cholesterol in blood exists as esters of the polyunsaturated fatty acids (Bloor, Blake and Bullen[9]). Although the exact metabolic pathways are still unknown, it has been demonstrated that the saturated and unsaturated fatty acids are metabolized differently (Hanahan[25], Phil, Bloch and Anker[40]). One may tentatively hypothecate that cholesterol esters of the unsaturated fatty acids, because of structure, are easier to metabolize and utilize in the biochemical degradation of cholesterol. Lack of availability of the polyunsaturated fatty acids, due to the insufficiency of dietary intake, directs the utilization of the available saturated and monounsaturated fatty acids in the esterification of cholesterol. The esters formed with saturated acids because of higher melting point, reduced solubility and other variable factors, tend to precipitate in the tissues of the body (Sinclair[46]).

Recent studies have demonstrated that fats high in saturated fatty acids, exogenous cholesterol and physiologic stress, with its concomitant rise in hormonal levels, all of which tend to induce hypercholesterolemia, accelerates polyunsaturated fatty acid deficiency (Sinclair[47]). When one realizes that the mammalian metabolism has but very limited or no capacity to synthesize linoleic acid, either from two carbon fragments or the enzymatic dehydrogenation of saturated or monounsaturated fatty acids (Bernhard, Steinhauser and Bullet[6], Mead, Steinberg and Howton[35]), it is easy to see how unbalanced lipid intake may not only tend to induce hypercholesterolemia, but also intensify the imbalance by furthering a withdrawal of polyunsaturated fatty acids from essential body depots, thus creating in addition to a deficiency state relative to these essential metabolites, a concurrent organic hypofunction. It is tempting to postulate that this may be one of the reasons for the hypophospholipidemia observed in so many cases of hypercholesterolemia.

Although linoleic acid serves as the dietary precursor of arachidonic acid, it is this tetraenoic acid which is required for most metabolic purposes (Griffith[23]). The mechanism of this synthesis is mediated by pyridoxine (Witten and Holman[52]) and the reaction could not be carried through to completion in the absence of this very essential biochemical catalyst. It has been demonstrated that while linoleic acid serves as the major source of arachidonic acid, it only serves as a source of docosahexaenoic acid in the heart, where it occurs in phospholipid form (Rieckehoff, Holman and Burr[43]). The trienoic acid, linolenic, on the other hand, serves as a source of clupanodonic acid and docosahexaenoic acid, both of which have been classified as essential unsaturated fatty acids (Widmer and Holman[51]).

Numerous investigators (Ahrens *et al.*[2,4], Bronte-Stewart *et al.*[11], Malmros and Wigand[34]) have determined that the replacement of animal fats in the diet with vegetable oils high in polyunsaturated fatty acids on an isocaloric basis results in rather prompt reduction of the circulating blood cholesterol.

Ahrens *et al.*, in a well defined series of experiments, determined that blood lipids could be significantly reduced

by the intake of vegetable oils containing a high degree of polyunsaturation and conversely that an increase in blood lipids occurred when dietary fats with a high degree of saturation were fed. Hydrogenation of corn and cottonseed oils resulted in findings identical to those observed with saturated fats. In this study it was also demonstrated that the glyceride moiety of vegetable oils was the fraction which exhibited the cholesterol reducing effect and not the nonsaponifiable fraction (Michaels[36]). Other investigators with a different experimental protocol have produced confirming data which is in accord with the basic findings (Anderson and Keys[5], Friskey, Michaels and Kinsell[20], Kinsell and Michael[31]). Others, however, have stated that the polyunsaturated fatty acids have little or no effect in reducing blood cholesterol, but that other substances, naturally occurring with the unsaturated fatty acids in vegetable oils, are the factors responsible for the observed reduction (Beveridge, Connell and Mayer[8]). Corn oil, with its sitosterol content, is an example of such material. As a matter of pertinent observation, the analysis of corn oil indicates that the nonsaponifiable fraction, consisting of sterols, tocopherols, phospholipids, carotene, and others, accounts for a maximum of 2% of the total weight. It is not consistent with experimental fact, however, that the minor concentrations of sitosterol (approximately 15 mg. per gm.) as found in corn oil are of sufficient magnitude to lower blood cholesterol significantly, particularly when substantial quantities of sitosterol must be administered at a therapeutic level to accomplish the desired reduction of abnormal cholesterol levels (Best and Duncan[7], Sachs and Weston[44]).

In an unreported series of experiments, it was determined that the addition of sitosterol, at a concentration of 15 mg. per gm. to safflower oil from which the naturally occurring plant sterols had been substantially removed did not exhibit any synergistic action and that equal portions of unfortified safflower oil and fortified safflower oil were required to influence the reduction of hypercholesterolemia (Worne and Smith[62]).

When determining the cholesterol depressant effect of the polyunsaturated fatty acids, it is not of advantage to administer vegetable oils which contain substantial concentrations of the saturated and monounsaturated fatty acids. As an example, both corn and cottonseed oils on analysis showed an average concentration of linoleic acid, which is approximately 50% of the total fatty acids. Saturated fatty acids, monounsaturated fatty acids and nonsaponifiables account for the balance. We, therefore, have a chemical system where the saturated and monounsaturated fatty acids are competing isochemically with the polyunsaturated fatty acids for the esterification of cholesterol. An additional important facet of this problem is the *in vitro* and *in vivo* stability and peroxide number of the experimental materials containing the polyunsaturates. It is not only necessary to stabilize the unsaturated fatty acids for storage and passage through the gastrointestinal mechanism, but sufficient physiologic antioxidants must be available to prevent premature oxidation of the highly labile double bonds in the tissues. Experimental evidence exists to show a concomitant rise in blood cholesterol when unsaturated fatty acids of sufficient peroxide values are fed (Worne and Smith[63]). Inasmuch as polyunsaturated fatty acids contain two or more points of unsaturation, they are extremely unstable, due to the ease of oxidation when exposed to air. The products of oxidative

rancidity are of the utmost importance, since they are not only toxic in themselves, but their presence in foods leads to oxidation and destruction of other essential substances (Clausen, Barnes and Burr[14], György *et al.*[24]). As a result, diets containing adequate concentrations of aqueous and lipid soluble vitamins may be converted into diets deficient in these substances (Pavcek and Schull[39]). This destruction of essential metabolites assumes even greater importance as more is understood concerning the need of pyridoxine(Tulpule and Williams[49]) for the conversion of the dienoic and trienoic acids into tetraenoic, pentaenoic and hexaenoic acids and the essentiality of Vitamin C and Vitamin E as physiologic antioxidants in protecting these essential metabolites from premature oxidation in the tissues.

One of the major problems which has arisen from the use of vegetable oils in the treatment of hypercholesterolemia is the high caloric intake necessary to accomplish the desired reduction, which results in undesirable weight gain. In addition, gastric intolerance and actual physical rejection to large volumes of oily preparations by the patient has added to the experimental variables.

In a series of previous studies from this laboratory, it was shown that the inclusion of the tetraenoic, pentaenoic and hexaenoic acids with linoleic acid (Lenic) exhibited a much higher level of therapeutic efficiency and that the velocity and magnitude of response in lowering blood cholesterol as well as in allergic diseases, degenerative diseases, mental diseases and other abnormalities studied was significantly greater when compared with the use of linoleic acid esters alone (Worne, Greenleaf and Tocci[55], Worne, Hausman and Scinta[56], Worne and Schneider[57,58], Worne and Silbert[59,60], Worne and Smith[61]).

Methods and Materials. Forty-two patients, both male and female, with and without hyperlipemia, were selected to study the effects of relatively pure ethyl linoleate, ethyl linolenate, methyl arachidonate, methyl clupanodonate and methyl docosahexaenoate on the etiopathogenesis of hypercholesterolemia. All of the patients used in this study were ambulatory and not under rigid dietary restrictions. Dietary fats, such as butter, margarine, eggs, milk and the visible fats in meat were maintained at a minimum. Subjects were instructed to trim off as much of the visible meat fat as possible. Each member of the experimental group kept a record of daily food intake for the period of the study. From this record, the fat calories in the food intake could be approximated. No patient with diabetes mellitus, thyroid disorders or renal disorders were accepted for inclusion in this study.

Blood samples for lipid analysis were drawn prior to therapy and every 30 days for a period of 90 days. In each of the cases studied, at least 4 blood specimens were collected. Each blood specimen was assayed for cholesterol by the method of Schoenheimer and Sperry[45], phospholipid levels were determined by the method of Subbarow and Fiske[19], total lipids by the method of Rappaport and Engelberg[41] and polyunsaturated fatty acids by the method of Holman and Hayes[29].

The patients were divided into 7 groups composed of 6 each. Group I received 1 gm. of ethyl linoleate 4 times a day. Group II received 4 gm. of ethyl linoleate 4 times a day. Group III received 1 gm. of ethyl linolenate 4 times daily. Group IV received 1 gm. of methyl arachidonate 4 times a day. Group V received 1 gm. of methyl clupanodonate 4 times a day. Group VI received 1 gm. of methyl docosahexaenoate 4 times a day and Group VII received 1 gm. of the following mixture 4 times a day:

ethyl linoleate	50. %
ethyl linolenate	12.5%
methyl arachidonate	12.5%
methyl clupanodonate	12.5%
methyl docosahexaenoate	12.5%

Results. Analysis of the results (Figs. 1A, 3C) showed that ethyl linolenate, 4 gm. per day, had little or no effect on total lipids, total cholesterol and phospholipid levels. Slight increases were observed in the linolenic, pentaenoic and hexaenoic acid fractions of the polyethenoic acids, but the altera-

tions were not significant and, therefore, not of statistical importance.

Ethyl linoleate (Fig. 1*B*) fed at the rate of 4 gm. per day also had little or no effect on total lipids, total cholesterol, phospholipids or the unsaturated fatty acids.

Ethyl linoleate fed at the rate of 16 gm. per day, on the other hand (Figs. 1*C*, 3*B*), resulted in a significant reduction in total lipids and total cholesterol. Phospholipid levels were altered so that an antiatherogenic ratio of cholesterol to phospholipids oc-

EFFECT OF POLYUNSATURATED FATTY ACID ESTERS INDIVIDUALLY, AND IN COMBINATION, UPON THE WHOLE BLOOD CONTENT OF TOTAL LIPIDS, PHOSPHOLIPIDS AND CHOLESTEROL ①

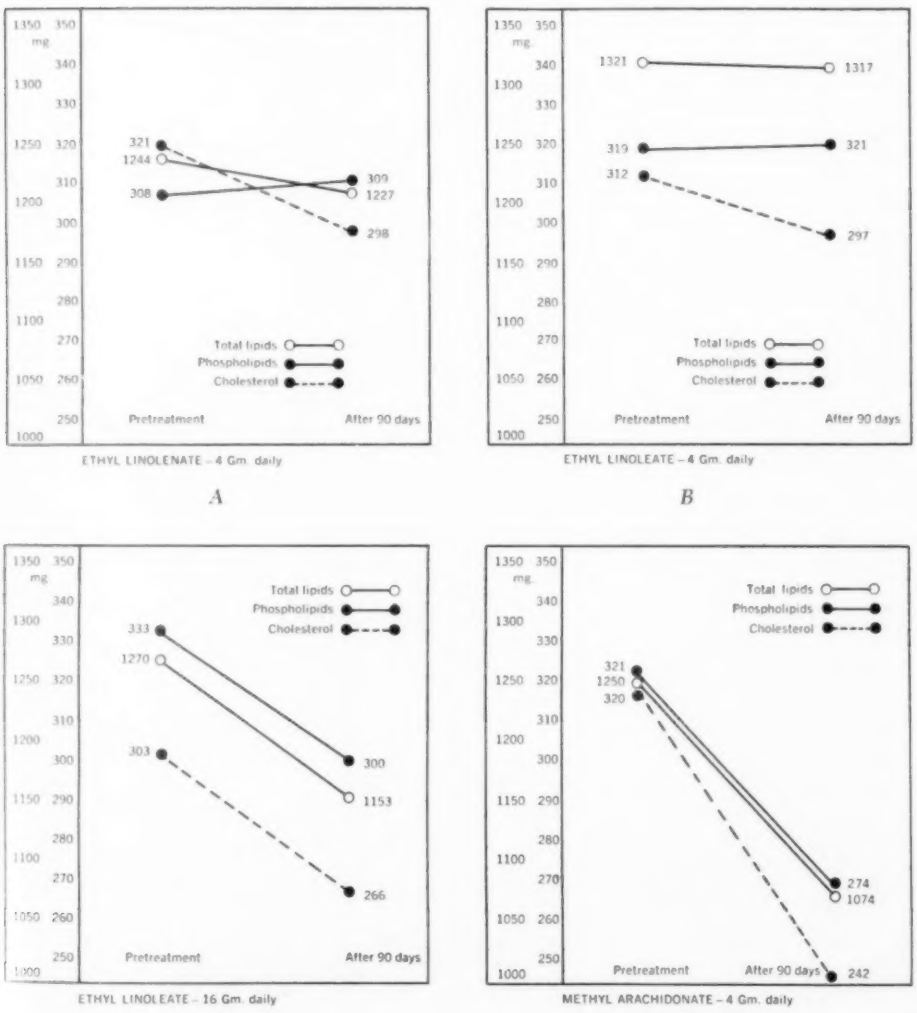


Fig. 1

curred. Evaluation of the unsaturated fatty acid fraction revealed that there was an increase in linoleic acid, accompanied by concomitant rises in the levels of the tetraenoic and hexaenoic acid fractions, indicating an enhanced rate of synthesis from the linoleic acid precursor.

Methyl arachidonate fed at the rate of 4 gm. per day also (Figs. 1*D*, 3*D*) resulted in significant reduction of total lipids and total cholesterol. Phopholipid levels were altered so that an antiatherogenic ratio of cholesterol to phospholipid occurred. Increases in the tetraenoic and hexaenoic acid fractions

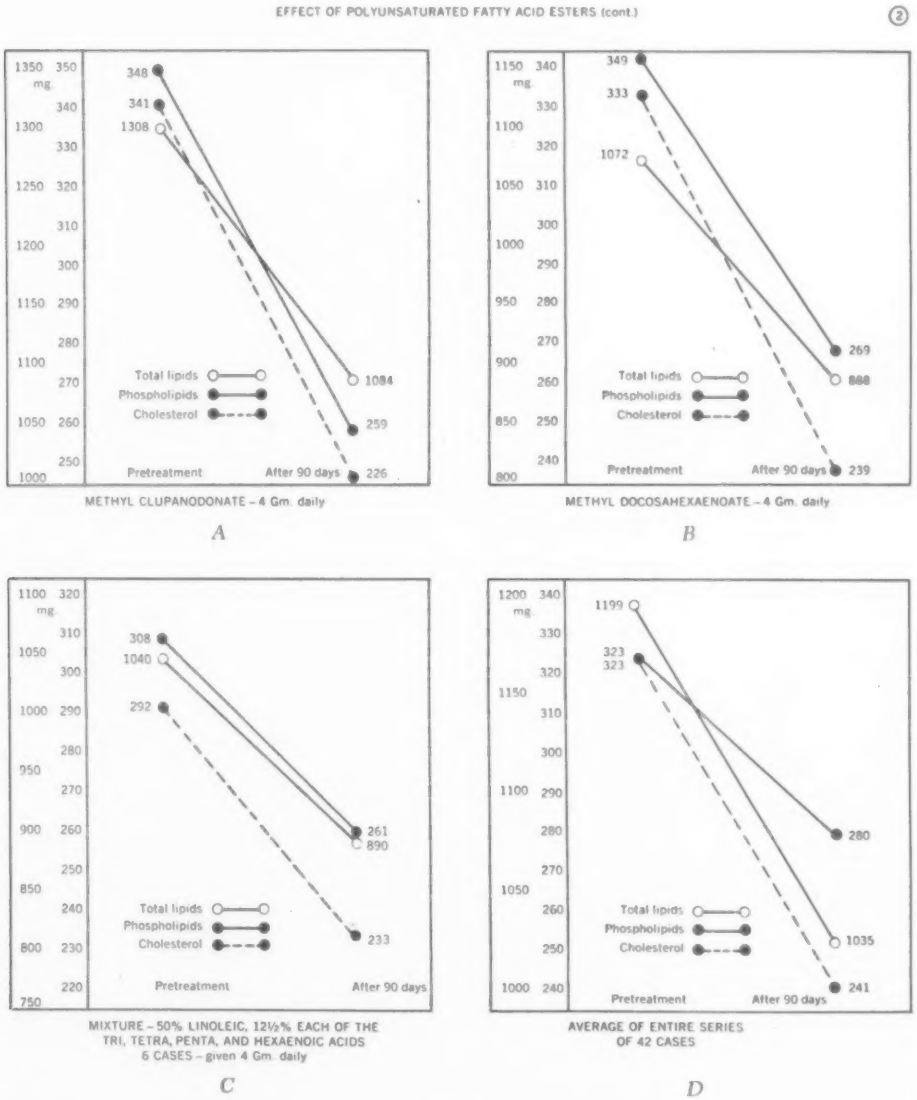


Fig. 2

of the polyethenoid acids were observed.

Methyl clupanodonate (Figs. 2A, 4A) when fed at a level of 4 gm. per day resulted in similar significant reductions of both total lipids and total cholesterol. Phospholipid levels were brought into a favorable antiathero-

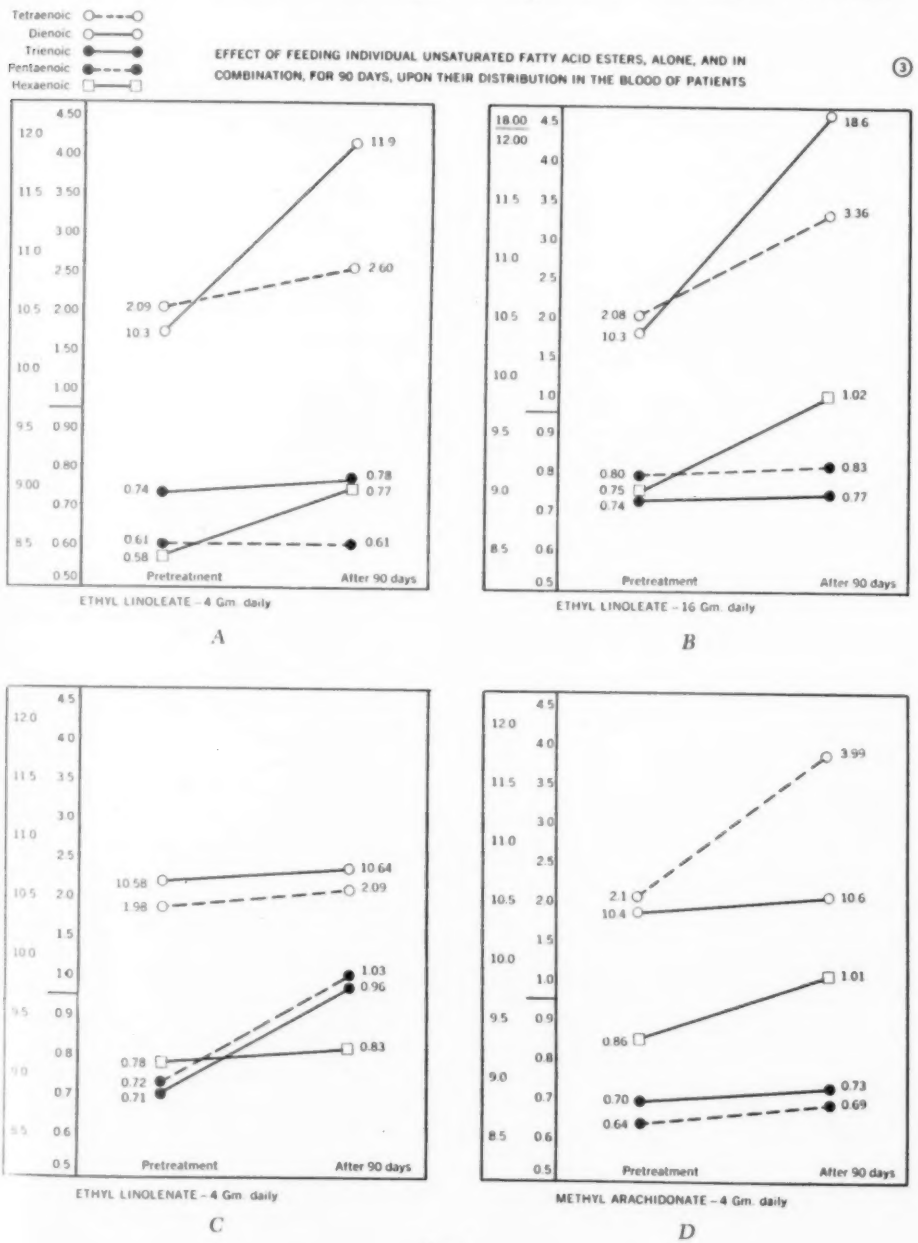


Fig. 3

genic ratio with cholesterol. The only alteration observed in the unsaturated fatty acids was in the pentaenoic acid fraction.

Methyl docosahexaenoate when fed at a level of 4 gm. per day (Figs. 2*B*, 4*B*) resulted also in a significant reduction of the total lipids and total

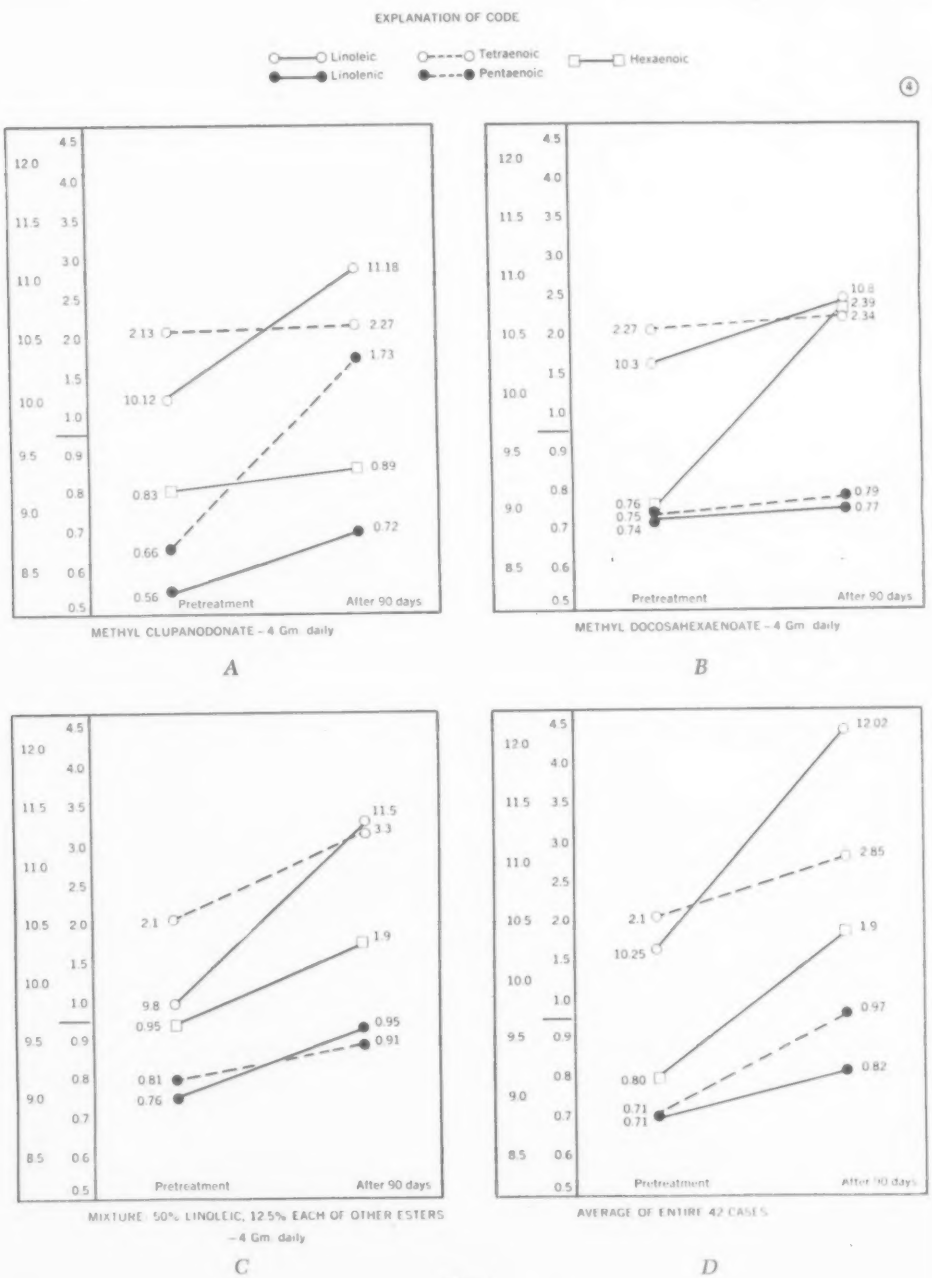


Fig. 4

cholesterol. Phospholipid levels were brought into a favorable antiatherogenic ratio with cholesterol. The level of the hexaenoic acid fraction of the polyethenoid fatty acids was markedly raised.

Mixed polyunsaturated fatty acid esters fed at a level of 4 gm. per day (Figs. 2*C*, 4*C*) resulted similarly in significant reductions in both total lipids and total cholesterol. Phospholipid levels were altered so that a favorable antiatherogenic ratio with cholesterol existed. All of the levels of the unsaturated fatty acids were raised.

The average results for the entire 42 cases are presented in Figs. 2*D* and 4 *D*.

Summary and Conclusions. Statistical analysis of the findings on the effect of the various polyunsaturated fatty acids showed a significant correlation between the number of double bonds in the fatty acid molecule and their effect on the blood lipids. Four grams per day of the 4, 5, and 6 double bonded fatty acids produced significant blood lipid changes reflected by reduced cholesterol levels and a more favorable cholesterol:phospholipid ratio. Four grams per day of ethyl linoleate (2 double bonds) or ethyl linolenate (3 double bonds) were without any significant effect in the reduction of total lipids or total cholesterol. It was not until 4 times the original dose, or 16 gm. of ethyl linoleate, was administered that adequate alterations in the blood lipids were effected. In addition to the cholesterol reduction, a concomitant improvement in the phospholipid levels was noted at this dosage level. It has been demonstrated that the ratio of serum cholesterol:lipid phosphorus has more significance than cholesterol levels alone (Ahrens and Kunkel[3]). The deposition of atheromatic plaques is apparently favored by a high cholesterol:phospholipid ratio, that is, a relatively lower phospholipid concentration (Duff[17]). It is accepted that phospholipids can effect the stabilization of colloidally dispersed plasma cholesterol, even when cholesterol is present in excessive quantities (Ladd, Kellner and Correll[32]). An increase in double bonds reduces significantly the total quantity of unsaturated fatty acids necessary to accomplish the desired reduction of abnormal lipid levels. There is no apparent difference in cholesterol depressant effect of the tetraenoic, pentaenoic or hexaenoic fatty acids. The combination of all of the polyunsaturated fatty acid esters gave rise to the same effects as the pure individual esters.

In 88% of the cases exhibiting signs of angina, intermittant claudication, and other signs of arterial insufficiency, there was objective evidence of gradual clinical improvement as the blood lipids were reduced to normal levels. In several patients with skin xanthomata elimination of these lipid lesions was observed concurrent with the reduction of the accompanying hyperlipemia or hypercholesterolemia. All of the patients except those in Group I and Group III reported an increased feeling of well being coupled with improved cerebration.

REFERENCES

1. **Aaes-Jorgensen, E.**, and **Dam, H.**: Brit. J. Nutrit., **8**, 290, 1954.
2. **Ahrens, E. H., Jr., Blankenhorn, D. H.**, and **Tsaltas, T. T.**: Proc. Soc. Exper. Biol. & Med., **86**, 872, 1954.
3. **Ahrens, E. H.**, and **Kunkel, H. G.**: J. Exper. Med., **90**, 409, 1949.

4. **Ahrens, E. H., Jr., Tsaltas, T. T., Hirsch, J.,** and **Insull, W., Jr.:** J. Clin. Invest., **34,** 918, 1955.
5. **Anderson, J. T.,** and **Keys, A.:** Fed. Proc., **13,** 449, 1954.
6. **Bernhard, K., Steinhauser, H.,** and **Bullet, F.:** Helv. Chim. Acta, **25,** 1313, 1942.
7. **Best, M. M.,** and **Duncan, C. H.:** Circulation, **14,** 344, 1956.
8. **Beveridge, J. R., Connell, W. F.,** and **Mayer, G. A.:** Canad. J. Biochem. and Physiol., **34,** 441, 1956.
9. **Bloor, W. R., Blake, A. G.,** and **Bullen, S. S.:** J. Allergy, **9,** 227, 1938.
10. **Borland, V. G.,** and **Jackson, C. M.:** Arch. Path., **11,** 687, 1931.
11. **Bronte-Stewart, B., Antonis, A., Eales, L.,** and **Brock, J. F.:** Lancet, **1,** 521, 1956.
12. **Burr, G. O.,** and **Burr, M. M.:** J. Biol. Chem., **82,** 345, 1929.
13. Iidem: Ibid., **86,** 587, 1930.
14. **Clausen, D. F., Barnes, R. H.,** and **Burr, G. O.:** Proc. Soc. Exper. Biol. & Med., **53,** 176, 1943.
15. **Decker, A. B., Fillerup, D. L.,** and **Mead, J. F.:** J. Nutrit., **41,** 5, 7, 21, 1950.
16. **Deuel, H. J., Jr., Martin, C. R.,** and **Alfin-Slater, R. B.:** Ibid., **57,** 297, 1955.
17. **Duff, G. L.:** Arch. Path., **20,** 81, 259, 1935.
18. **Evans, H. M., Lepkovsky, S.,** and **Murphy, E. A.:** J. Biol. Chem., **106,** 445, 1934.
19. **Fiske, C. H.,** and **Subbarow, Y.:** Ibid., **66,** 375, 1925.
20. **Friskey, R. W., Michaels, G. D.,** and **Kinsell, L. W.:** Circulation, **12,** 492, 1955.
21. **Greenberg, S. M., Calbert, C. E., Deuel, H. J., Jr.,** and **Brown, J. B.:** J. Nutrit., **45,** 521, 1951.
22. **Greenberg, S. M., Calbert, C. E., Savage, E. E.,** and **Deuel, H. J., Jr.:** Ibid., **41,** 473, 1950.
23. **Griffith, W. H.:** J. Am. Med. Assn., **164,** 411, 1957.
24. **György, P., Tomarelli, R., Ostergard, R. P.,** and **Brown, J. B.:** J. Exper. Med., **76,** 413, 1942.
25. **Hanahan, D. J.:** J. Biol. Chem., **211,** 313, 1954.
26. **Hansen, A. E., Holmes, S. G.,** and **Wiese, H. F.:** Texas Rep. Biol. Med., **9,** 555, 1951; Chem. Abst., **47,** 9447, 1953.
27. **Hansen, A. E., Sinclair, J. G.,** and **Wiese, H. F.:** J. Nutrit., **52,** 541, 1954.
28. **Hansen, A. E.,** and **Wiese, H. F.:** Tr. Soc. Pediat. Res., Am. J. Dis. Child., **69,** 325, 1945.
29. **Holman, R. T.,** and **Hayes, H.:** Methods of Biochemical Analysis, **4,** 1957.
30. **Hume, E. M., Nunn, L. C. A., Smedley-Maclean, I.,** and **Smith, H. H.:** Biochem. J., **32,** 2162, 1938.
31. **Kinsell, L. W.,** and **Michael, G. D.:** Fed. Proc., **14,** 661, 1955.
32. **Ladd, A. T., Kellner, A.,** and **Correll, J. W.:** Ibid., Part I, **8,** 360, 1949.
33. **Maeder, E. C.:** Anat. Record, **70,** 73, 1937; Chem. Abst., **32,** 2178, 1938.
34. **Malmros, H.,** and **Wigand, G.:** Minnesota Med., **38,** 864, 1955.
35. **Mead, J. F., Steinberg, G.,** and **Howton, D. R.:** J. Biol. Chem., **205,** 683, 1953.
36. **Michaels, G. D.:** Am. J. Clin. Nutrit., **3,** 247, 1955.
37. **Panos, T. C.,** and **Finerty, J. C.:** J. Nutrit., **49,** 397, 1953.
38. Iidem: Ibid., **54,** 315, 1954.
39. **Pavcek, P. L.,** and **Schull, G. M.:** J. Biol. Chem., **146,** 351, 1942.
40. **Phil, A., Bloch, K.,** and **Anker, H. S.:** Ibid., **183,** 441, 1950.
41. **Rappaport, F.,** and **Engelberg, H.:** J. Lab. & Clin. Med., **28,** 1767, 1943.
42. **Reid, M. E.:** Fed. Proc., **14,** 448, 1955.
43. **Rieckehoff, I. G., Holman, R. T.,** and **Burr, G. O.:** Arch. Biochem., **20,** 331, 1949.
44. **Sachs, R. A.,** and **Weston, R.:** Arch. Internat. Med., **97,** 738, 1956; Chem. Abst., **50,** 14097, 1956.
45. **Schoenheimer, R.,** and **Sperry, W. M.:** J. Biol. Chem., **106,** 745, 1934.
46. **Sinclair, H. M.:** Roy. Soc. Health J., **77,** 234, 1957.
47. Idem: Lancet, **1,** 381, 1956.
48. **Smedley-Maclean, I.,** and **Nunn, L. C. A.::** Biochem. J., **34,** 884, 1940.
49. **Tulpule, P. G.,** and **Williams, J. N., Jr.:** J. Biol. Chem., **217,** 229, 1955.
50. **Turpeinen, O.:** J. Nutrit., **15,** 351, 1938.
51. **Widmer, C., Jr.,** and **Holman, R. T.:** Arch. Biochem., **25,** 1, 1950.
52. **Witten, P. W.,** and **Holman, R. T.:** Ibid., **41,** 266, 1952.
53. **Wood, J. D.,** and **Migicovsky, B. B.:** Canad. J. Biochem. and Physiol., **34,** 861, 1956.
54. **Worne, H. E.:** New Jersey Vet. Med. Assn., April, 1956.

55. **Worne, H. E., Greenleaf, H. E.,** and **Tocci, F. P., Sr.:** Arch. Research, **1**, 27, 1954.
56. **Worne, H. E., Hausman, S. W.,** and **Scinta, L. A.:** Ibid., **1**, 7, 1954.
57. **Worne, H E.,** and **Schneider, J.:** Ibid., **1**, 12, 1954.
58. Iidem: Ibid., **1**, 21, 1954.
59. **Worne, H. E.,** and **Silbert, N. E.:** Ibid., **1**, 16, 1954.
60. Iidem: J. Appl. Nutrit., **8**, 350, 1955.
61. **Worne, H. E.,** and **Smith, L. W.:** Antibiot. Med. & Clin. Therap., **4**, 515, 1957.
62. Iidem: Unpublished research.
63. Iidem: To be published.

SUMMARIO IN INTERLINGUA

Le Effectos De Certe Pur Esteres De Polynonsaturate Acidos Grasse A Catena Longe Super Le Lipidos Del Sanguine Human

Studios Preliminar Super Le Uso De Polynonsaturate Acidos Grasse In Le Tractamento De Atherosclerosis

Le analyse statistic del constatationes de recercas relative al effecto de varie polynonsaturate acidos grasse revelava un correlation significative inter le numero del ligamines duple in le molecula de acido grasse e le effecto producite per ille substantias in le lipidos del sanguine. Doses diurne de 4 grammas de acidos grasse a 4, 5, e 6 ligamines duple produceva significative alterationes in le lipidos del sanguine, reflectite in reducite nivellos de cholesterol e un plus favorabile proportion de cholesterol a phospholipido. Dosages diurne de 4 grammas de linoleato ethylic (2 ligamines duple) o de linolenato ethylic (3 ligamines duple) esseva sin effecto significative con respecto al reduction del lipidos total o del cholesterol total. Solmente quando 4 vices le dosage original, *i.e.* 16 g de linoleato ethylic, esseva administrate, il occurreva adequate alterationes in le lipidos del sanguine. A parte le reduction del cholesterol, un melioration concomitante del nivellos phospholipidic esseva notate a iste nivello de dosage. Il ha essite demonstrate (per Ahrens e Kunkel[3]) que le proportion inter cholesterol e phosphoro lipidic in le sero es plus significative que le nivellos del cholesterol *per se*. Le deposition de placas atheromatic es apparentemente promovite per un alte proportion inter cholesterol e phospholipido, *i.e.* per un relativemente basse concentration phospholipidoc (Duff[17]). Es acceptate como facto que phospholipidos es capace a effectuar le stabilisation de cholesterol que es dispergite como colloide in le plasma, mesmo quando le cholesterol es presente in quantitates excessive (Ladd, Kellner, e Correll[32]). Un augmento del numero de ligamines duple reduce significativemente le quantitate total de nonsaturate acidos grasse que es requirite pro effectuar le desirate reduction de anormal nivellos lipidic. Il existe nulle apparente differentia in le depression de cholesterol effectuate per le tetra-, penta-, o hexaenoic acidos grasse. Le combination de omne le esteres de polynonsaturate acidos grasse produceva le mesme effectos como le pur esteres individual.

In 88% del casos con signos de angina, claudication intermittente, e altere provas de insufficientia arterial, un gradual melioration clinic esseva objectivemente evidente durante que le lipidos del sanguine esseva reducite a nivellos normal. In plure patientes con xanthomas cutanee, le elimination de iste lesiones lipidic esseva observate in concomitantia con le reduction del accompaniante hyperlipemia o hypercholesterolemia. Omne le patientes, con le exception de illes in gruppo I e gruppo III reportava un augmentate sensation de benesser insimul con un meliorate cerebration.

RENAL FUNCTION IN LIVER DISEASE AND MALNUTRITION

By Ivan Duque, M.D.
SENIOR RESIDENT OF INTERNAL MEDICINE

Ivan Jimenez, M.D.
ASSISTANT PROFESSOR OF PHYSIOLOGY

AND

Guillermo Latorre, M.D.
PROFESSOR AND CHAIRMAN OF PHYSIOLOGY

(From the Departments of Internal Medicine and Physiology, University of Antioquia Medical School, Medellin, Colombia, S.A.)

Disturbances of water metabolism and renal function, which usually appear later in the course of liver disease and without the presence of organic lesions of the kidney, are commonly observed in patients with acute or chronic liver diseases.

Some studies have been made attempting to find a satisfactory explanation for the changes of water metabolism in liver diseases. Of primary importance there have been accepted a series of disturbances of renal hemodynamics and tubular transport, aside from other important factors, such as the action of the antidiuretic hormone of the posterior pituitary or a defect in the management of sodium by the renal tubules (Litchman[9]).

Fiessinger, Varay, Gadjos and Panayatopoulas[6] measured the glomerular filtration rate (GFR) by endogenous creatinine in 14 patients with liver cirrhosis and found that in 9 cases it was depressed and in 5, normal or increased. Cachera, Darnis and Lubetzki[3] found in 27 determinations, performed on 16 patients with liver cirrhosis, a depression of 60% of the GFR, having as a control determinations effected in 11 normal subjects.

Farnsworth and Krakusin[4], and Patek, Mankin, Colcher, Lowell and Earle[11], working with inulin and sodium para-aminohippurate (PAH) in patients with liver cirrhosis and edema, found low, high or normal GFR and renal plasma flows (RPF). Leslie, Johnston and Krakusin[8], in patients in whom ascites had never been present, or not present to a degree that required paracentesis, found a normal or high renal function. In patients who required paracentesis but at the time of study had no significant ascites, all measurements were normal. In patients who were rapidly accumulating ascites, renal function was depressed.

In acute infectious hepatitis, Farquhar[5] found a depression of the urea clearance and tubular concentration power, and an increase of urinary proteins, erythrocytes and casts.

In this paper we present the results of 37 renal clearances that were done in 13 patients who suffered malnutrition but without evidence of liver insufficiency, 13 cases of malnutrition with laboratory and clinical evidence of liver deficiency, 7 patients with liver cirrhosis at different stages of the disease, 2 patients with carcinoma of the liver and 2 patients with acute infectious hepatitis.

Material and Methods. Thirty-seven patients, all males 15 to 84 years of age, from

the medical wards of the Hospital de San Vicente de Paúl, Medellín, Colombia, were selected on the basis of history, physical and pathological (biopsy) examinations, and liver function tests which showed evidence of liver damage or malnutrition.

These patients fasted the day of the experiments and to insure adequate urine flow, 800 to 1000 ml. of water, given in 4 doses 15 minutes apart, were administered orally before the tests. GFR was measured by the clearance of the inulin, and RPF by the clearance of the PAH. Renal clearances were determined in several periods of 15 to 20 minutes each, using an intravenous priming injection of 25 mg. of inulin and 30 mg. of PAH per kg. of body weight dissolved in 10 ml. of saline, and subcutaneous sustaining injection of 100 mg. of inulin and 30 mg. of PAH dissolved in 25 ml. of saline; venous samples were drawn from the basilic vein and urine obtained through a Malecot Catheter No. 16 or No. 18. Standard methods of determinations were used (Findley and White[7], Rolf, Surtshin and White[14]). Each datum is the mean of 3 clearance periods. Results are given corrected to 1.73 M^2 of surface area (McIntosh, Moller and Van Slyke[10]).

TABLE 1.—SERUM PROTEIN LEVELS AND RENAL FUNCTION MEASUREMENT VALUES IN PATIENTS WITH MALNUTRITION AND CLINICAL AND LABORATORY EVIDENCE OF LIVER INSUFFICIENCY.

Case No.	Age Years	Weight kg.	Surface Area M^2	Serum Proteins			Renal Function Tests		
				Total gm. %	Albumin gm. %	Globulin gm. %	G.F.R.	R.P.F.	F.F.
3	42	51	1.52	6.00	3.95	2.05	82.8	734.0	.113
5	32	48	1.48	7.45	4.60	2.85	304.0	1,561.0	.195
9	40	47	1.42	5.00	3.20	1.80	403.0	1,133.0	.356
10	45	56	1.58	6.85	3.90	1.95	218.8	902.0	.243
11	47	48	1.48	5.60	3.20	2.40	311.0	980.0	.318
15	50	50	1.56	6.10	3.20	2.90	376.0	805.0	.467
18	33	56	1.68	5.80	3.95	1.85	286.7	1,422.0	.202
19	35	50	1.52	4.15	2.60	1.55	211.5	449.0	.425
20	55	51	1.53	5.22	3.83	1.39	268.5	812.0	.327
22	53	43	1.39	5.10	2.60	2.50	294.0	874.0	.336
26	56	50	1.68	5.90	4.05	1.85	222.0	567.0	.392
27	57	45	1.45	5.80	3.70	2.10	210.0	1,070.0	.196
32	55	50	1.52	6.50	4.35	2.15	655.0	1,503.0	.435

Results. I. PATIENTS WITH MALNUTRITION AND CLINICAL AND LABORATORY EVIDENCE OF LIVER INSUFFICIENCY (TABLE 1). In this group the GFR measurement values ranged from 82.8 to 655.0 ml. per minute. RPF ranged from 449.0 to 1,568.0 ml. per minute. Filtration fraction (FF) varied from 11.3 to 46.7%. GFR was slight or considerably increased in all patients, but one had a depressed clearance and died 4 days after the renal function study. RPF was increased in 8 patients, depressed in 2 and normal in 3. FF was depressed in the patient who died, increased in 8 and normal in 4.

II. PATIENTS WITH MALNUTRITION WITHOUT CLINICAL AND LABORATORY EVIDENCE OF LIVER INSUFFICIENCY (TABLE 2). In this group the GFR measurement values ranged from 174.0 to 408.0 ml. per minute. RPF ranged from 546.0 to 1,568.0 ml. per minute. FF varied from 24.6 to 45.5%. GFR was increased in all the patients. RPF and FF was increased in 8, normal in 5.

III. PATIENTS WITH CIRRHOSIS OF THE LIVER (TABLE 3). GFR measurement values ranged from 124.8 to 309.0 ml. per minute, and RPF from 298.5 to 1,380.0 ml. per minute. FF varied between 14.7 and 68.1%. GFR was increased in all but one, which was normal. RPF was increased in all but one

which was depressed. FF was normal in 2, depressed in 2, and increased in 3 patients.

IV. PATIENTS WITH ACUTE INFECTIOUS HEPATITIS. (TABLE 4). GFR measurement values were high in both patients (323.0 and 490.0 ml. per minute). RPF was high in one patient (1,253.0 ml. per minute) and normal in the second one (762.0 ml. per minute). FF was 25.7 and 63.0%, respectively.

V. PATIENTS WITH CARCINOMA OF THE LIVER (TABLE 5). GFR measurement values were high in both cases (318.5 and 241.5 ml. per minute). RPF was high in one case (849.0 ml. per minute) and normal in the other one (663.0 ml. per minute). FF was normal in both (37.5 and 38.8%, respectively).

Discussion. There is evidence of disturbances of renal function in patients with liver diseases and malnutrition, though the interpretation and correlation of the alterations are difficult, owing to the many physiological effects that might contribute to the functional impairment.

In malnourished patients with clinical and laboratory evidence of liver insufficiency, 12 out of 13 cases presented a high GFR, associated with hypoalbuminemia, and in 9 of them a high

TABLE 2.—SERUM PROTEIN LEVELS AND RENAL FUNCTION MEASUREMENT VALUES IN PATIENTS WITH MALNUTRITION WITHOUT CLINICAL AND LABORATORY EVIDENCE OF LIVER INSUFFICIENCY.

Case No.	Age Years	Weight kg.	Surface Area M^2	Serum Proteins			Renal Function Tests		
				Total gm. %	Albumin gm. %	Globulin gm. %	G.F.R.	R.P.F.	F.F.
12	35	50	1.67	5.00	3.00	2.00	335.0	998.0	.336
13	36	55	1.59	5.22	4.05	1.17	318.1	1,293.0	.246
14	29	51	1.58	4.25	2.50	1.75	379.0	1,320.0	.287
17	84	50	1.54	3.70	2.10	1.60	174.0	546.0	.319
21	37	46	1.51	4.25	2.50	1.75	354.5	780.0	.455
23	31	55	1.62	4.15	2.10	2.05	316.0	1,255.0	.252
24	23	47	1.44	6.50	4.35	2.15	408.0	1,568.0	.260
25	60	58	1.75	2.60	1.60	1.00	212.2	843.0	.252
28	32	48	1.50	5.22	3.00	2.22	283.0	962.0	.294
29	31	50	1.50	5.10	3.32	1.78	318.0	1,046.0	.304
33	64	45	1.41	5.47	3.10	2.37	267.0	782.0	.341
35	42	50	1.66	5.80	3.70	2.10	200.0	800.0	.250
36	51	52	1.60	5.90			330.5	785.0	.421

TABLE 3.—SERUM PROTEIN LEVELS AND RENAL FUNCTION MEASUREMENT VALUES IN PATIENTS WITH CIRRHOSIS OF THE LIVER.

Case No.	Age Years	Weight kg.	Surface Area M^2	Serum Proteins			Renal Function Tests		
				Total gm. %	Albumin gm. %	Globulin gm. %	G.F.R.	R.P.F.	F.F
1	15	33	1.37	4.90	3.10	1.80	124.8	850.0	.147
2	35	66	1.69	6.50	3.45	2.15	307.0	1,007.0	.283
4	27	53	1.62	6.00	3.70	2.30	211.5	1,085.0	.195
8	62	44	1.43	5.60	3.45	2.15	270.2	861.0	.314
16	24	47	1.48	5.00	3.00	2.00	309.0	1,380.0	.224
30	15	35	1.19	6.00	4.15	1.85	157.3	939.0	.168
34	56	61	1.80	3.70	2.10	1.60	203.0	298.5	.681

RPF; it is reasonable to think that modifications of RPF are secondary to the disturbances of liver function (Popper and Schaffner[13]). Two patients that presented a normal RPF and another 2 with a depressed RPF were in a poor nutritional state, and under those circumstances there is a generalized endocrinological hypoactivity with insufficient utilization of hormones (Paullada[12]); it seems possible that results in these 4 cases are associated with this fact.

liver in different stages of the disease, we found clearance measurement values higher than those obtained by other observers. In 6 out of the 7 patients studied the GFR was high, and normal in the other 1; the RPF was high in 6 and depressed in 1. In this group of patients the nutritional state was very poor and, in all but one, hypoalbuminemia was present.

There have been found in acute infectious hepatitis morphologic and functional changes in the kidney in

TABLE 4.—SERUM PROTEIN LEVELS AND RENAL FUNCTION MEASUREMENT VALUES IN PATIENTS WITH ACUTE INFECTIOUS HEPATITIS.

				Serum Proteins			*Renal Function Tests*		
Case No.	*Age Years*	*Weight kg.*	*Surface Area M^2*	*Total gm. %*	*Albumin gm. %*	*Globulin gm. %*	*G.F.R.*	*R.P.F.*	*F.F.*
7	15	35	1.16	7.00	5.35	1.65	323.0	1,253.0	.257
31	14	34	1.20	6.50	4.35	2.15	490.0	762.0	.630

TABLE 5.—SERUM PROTEIN LEVELS AND RENAL FUNCTION MEASUREMENT VALUES IN PATIENTS WITH CARCINOMA OF THE LIVER.

				Serum Proteins			*Renal Function Tests*		
Case No.	*Age Years*	*Weight kg.*	*Surface Area M^2*	*Total gm. %*	*Albumin gm. %*	*Globulin gm. %*	*G.F.R.*	*R.P.F.*	*F.F.*
6	58	47	1.45	5.22	3.20	2.02	318.5	849.0	.375
37	48	58	1.72	6.10	4.75	1.35	241.5	663.0	.388

In malnourished patients in whom laboratory evidence of liver deficiency was not present, the GFR was high in all of them and the RPF also high in 8 cases out of 13. We think these changes are associated with some degree of liver insufficiency owing to the poor nutritional state, not enough to produce laboratory evidence of liver deficiency. According to this interpretation the alterations of GFR and RPF are secondary to disturbances of the hormonal control of the liver in malnutrition.

In 7 patients with cirrhosis of the accord with urinary findings (Benda, Rissel and Stefenelli[1,2]). In 2 cases that we studied in the acute phase, both presented a high GFR, possibly due to the changes in capillary permeability (Farquhar[5]), since RPF, proteins, and albumin were normal.

In 2 patients with carcinoma of the liver, GFR was high and RPF was normal. The alteration of GFR was possibly due in one case to the hypoalbuminemia (Case 6), and in the other one the possibility exists of glomerular damage, as evidenced by urine analysis.

Summary. Thirty-seven renal clearance measurements were performed on 37 patients with liver diseases and malnutrition, selected by physical and laboratory examination, weight and height.

Most of the patients presented disturbances of renal functional tests, essentially characterized by a high glomerular filtration rate, renal plasma flow, and filtration fraction. The modifications observed are related to hypoproteinemia, hypoalbuminemia and to a depression of the endocrine metabolism.

REFERENCES

1. **Benda, L., Rissel, E.,** and **Stefenelli, N.:** Deutsche med. Wchnschr., **79,** 1035, 1954.
2. Iidem: Ibid., **79,** 1091, 1954.
3. **Cachera, R., Darnis, F.,** and **Lubetzki, J.:** Sem. Hosp. Paris, **70,** 3606, 1953.
4. **Farnsworth, E. B.,** and **Krakusin, J. S.:** J. Lab. & Clin. Med., **33,** 1545, 1948.
5. **Farquhar, J. D.:** Am. J. Med. Sci., **218,** 291, 1949.
6. **Fiessinger, N., Varay, A., Gadjos, A.,** and **Panayatopoulas, E.:** Bull. et Mem. Soc. Med. Hosp. Paris, **54,** 490, 1938.
7. **Findley, T.,** and **White, H. L.:** Proc. Soc. Exper. Biol. & Med., **45,** 623, 1940.
8. **Leslie, S. H., Johnston, B.,** and **Krakusin, J. S.:** J. Clin. Invest., **30,** 1200, 1951.
9. **Litchman, S. S.:** Am. J. Digest. Dis., **21,** 108, 1954.
10. **McIntosh, J. F., Moller, R.,** and **Van Slyke, D. D.:** J. Clin. Invest., **6,** 467, 1929.
11. **Patek, A. J., Mankin, H., Jr., Colcher, H., Lowell, A.,** and **Earle, D. P., Jr.:** J. Clin. Invest., **27,** 135, 1948.
12. **Paullada, J. J.:** Revista de Investig. Clínica México, **7,** 29, 1955.
13. **Popper, H.,** and **Schaffner, F.:** Liver: Structure and Function. New York, Toronto, London: The Blakiston Division McGraw-Hill Book Company, Inc., 1957.
14. **Rolf, D., Surtshin, A.,** and **White, H. L.:** Proc. Soc. Exper. Biol. & Med., **72,** 351, 1949.

SUMMARIO IN INTERLINGUA

Le Function Renal In Morbo Hepatic E In Malnutrition

Trenta-septe mesurationes del clearance renal esseva effectuate in 37 patientes con morbo hepatic e malnutrition, seligite per examines physic e laboratorial e secundo lor peso e lor altor.

Le majoritate del patientes exhibiva disturbationes in le tests del functiones renal. Istos esseva essentialmente characterisate per acceleration del filtration glomerular e del fluxo de plasma renal e per un augmento del fraction de filtration. Le modificationes observate es relationate con hypoproteinemia, hypoalbuminemia, e un depression del metabolismo endocrin.

ASCITES: ETIOLOGIC CONSIDERATIONS WITH EMPHASIS ON THE VALUE OF SEVERAL LABORATORY FINDINGS IN DIAGNOSIS

By Morton E. Tavel, M.D.
RESIDENT IN INTERNAL MEDICINE, PHILADELPHIA GENERAL HOSPITAL
PHILADELPHIA, PENNSYLVANIA

(From the Department of Pathology, Veterans Administration Hospital, Indianapolis, Indiana)

What laboratory findings aid us in an attempt to diagnose the etiology of ascites, and what is their relative importance? Not infrequently the clinician is confronted by a patient in whom, after a thorough history and physical examination, the underlying cause of this common manifestation, ascites, remains obscure. Perhaps even more often, he encounters a case wherein ascites exists in the presence of one fairly obvious potential cause but he desires to know whether there exists another, more occult, etiologic factor to which the presence of ascites could be partially or wholly attributed. The clinician eventually seeks aid by such means as blood studies and diagnostic paracentesis, many times only to become confused or at best uninformed by the results of the various observations and studies obtained. This difficulty is quite understandable in view of the incomplete information found on many facets of this subject in standard textbooks of medicine and pathology and the relatively small amount of work published during the past century. Thus, it is the purpose to review this subject herein and to make use of data obtained from cases in which the diagnosis was ultimately discovered, in an attempt to correlate several current laboratory tests with each common cause of ascites. When possible, an endeavor will be made to compare the present findings with those of earlier investigators. Several of the rarer causes of ascites will be discussed briefly.

Clinical Material. Utilizing necropsy material of recent months and case records from as far back as 15 years taken from the Indiana University Medical Center, Indianapolis Veterans and General Hospitals, the author reviewed 142 cases manifesting ascites. The ascitic fluid was studied for gross appearance; specific gravity, utilizing an ordinary urinometer; total protein; total cell and differential counts; and malignant cells, using both the cytologic smear and cell block techniques.

Also tabulated were serum proteins (albumin and globulin) and Bromsulphalein (BSP) dye retention for 45 minutes using 5 mg. per kg. body weight. Both ascitic and serum protein levels were obtained by the biuret and salting-out methods.

Many of the subjects were hospitalized on more than one occasion and had repeated blood and ascitic fluid studies. In 15 cases, ascitic fluid specimens also were obtained within 24 hours postmortem and studied for appearance, specific gravity, and protein content. Included in the present series are the results of all laboratory studies, thus accounting for the discrepancy between total number of cases in each disease group and the number of times each study was made. The results are summarized in the tables below.

It was decided to include only those cases wherein the diagnosis was established by necropsy, biopsy, culture, or unequivocal clinical findings, excluding those in which more than one causal factor was suspected, or in which the diagnosis remained obscure due to inadequate follow-up. The only possible exception to this selection would be portal vein thrombosis, which occurred secondary to ascites-causing diseases in 3 cases included in the present series. Since portal thrombosis almost always denotes the existence of another disease and is only rarely

TABLE 1.—THE RESULTS OF THE BLOOD CHEMISTRY STUDIES IN THE VARIOUS DISEASES ASSOCIATED WITH ASCITES

	Serum Albumin (gm.%)								*Serum Globulin (gm.%)*								*% BSP Dye Retention (45 minutes)*						
Disease (Number of cases studied)	1.8–2.0	2.1–2.5	2.6–3.0	3.1–3.5	3.6–4.0	4.1–4.5	4.5–5.0	5.1–5.4	0.8–2.0	2.1–2.5	2.6–3.0	3.1–3.5	3.6–4.0	4.1–4.5	4.6–5.0	5.1–5.8	0–5	6–10	11–20	21–30	31–40	41–50	51–60
Cirrhosis (47)	8	21	43	23	6	1	0	0	8	10	16	20	22	18	5	3	0	3	6	6	12	2	3
Neoplasm (53)	0	8	8	14	7	0	0	0	12	10	10	2	4	1	0	0	2	0	1	1	1	1	0
Congestive Heart Failure (24)	0	2	3	7	4	3	1	0	9	1	8	1	1	0	0	0	0	1	3	0	2	0	0
Tuber-culosis (14)	0	0	2	2	2	3	0	1	0	2	2	4	2	0	0	0	4	0	0	0	0	0	0
Nephrosis (1)	2	0	1	1	0	1	0	0	2	2	1	0	0	0	0	0	–	–	–	–	–	–	–
Peritonitis (2)	0	0	0	1	0	0	0	0	1	0	0.	0	0	0	0	0	–	–	–	–	–	–	–
Chylous Ascites Idiopathic (1)	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	–	–	–	–	–	–	–

TABLE 2.—THE RESULTS OF THE VARIOUS STUDIES PERFORMED ON THE ASCITIC FLUID FOUND IN EACH DISEASE

Disease (*No. of cases studied*)	*Appearance*					*Specific Gravity*					*Total Protein Concentration (gm. %)*										*Cell Count**						
																					WBC			*RBC*			
	bloody	greenish	milky	yellow to amber	purulent	1.003–5	1.006–10	1.011–15	1.016–20	1.021–23	0.1–1.0	1.1–1.5	1.6–2.0	2.1–2.5	2.6–3.0	3.1–3.5	3.6–4.0	4.1–4.5	4.6–5.0	5.1–5.8	0–2	2–4	4+	0–5	5–10	10–15	15+
Cirrhosis (47)	2	0	0	61	0	2	22	11	2	0	25	4	6	3	0	0	0	0	0	0	22	1	1	19	1	0	0
Neoplasm (53)	15	5	4	34	0	1	8	6	11	1	5	5	3	3	3	4	4	0	0	3	10	1	0	7	0	2	2
Congestive Heart Failure (24)	2	3	1	17	0	0	12	10	1	0	0	2	1	3	4	4	1	1	0	0	9	0	0	7	0	1	1
Tuberculosis (14)	0	0	0	7	0	0	0	2	7	0	0	0	0	0	0	1	2	2	0	2	4	0	0	3	1	1	0
Nephrosis (1)	0	0	2	1	0	0	4	0	0	0	2	1	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0
Peritonitis (2)	0	0	0	1	1	0	0	0	1	0	0	0	0	0	0	0	0	1	1	0	–	–	–	–	–	–	–
Chylous Ascites Idiopathic (1)	0	0	1	0	0	–	–	–	–	–	0	0	0	0	0	0	0	0	1	0	–	–	–	–	–	–	–

*Each unit represents 1,000

the sole cause of ascites, this condition is best considered, for our purposes, as a manifestation of an underlying disease rather than as a separate entity.

Of the 142 cases studied, 57 ultimately went to necropsy. An additional 29 were diagnosed by surgical or biopsy specimens; and 4 by culture of tubercle bacilli from the ascitic fluid. A total of 90 cases (63%) were diagnosed, therefore, by these specific objective criteria; the remaining 52 were diagnosed by clinical means. The results obtained from these two groups did not differ significantly.

DEFINITION AND CAUSES OF ASCITES. Ascites is defined as the collection of free fluid in the peritoneal cavity. A subdivision of this category is termed chylous ascites, in which the fluid resembles chyle, containing a visible amount of milky-appearing fat. In the remainder of cases, the fluid is variable in appearance, ranging from clear to cloudy, and from straw-colored to grossly bloody.

Disease groups which have been said to cause ascites may be listed, arbitrarily, as follows (Abrahams[1], Cabot[6], Mensh and Banks[41]):

1. Diseases of the Heart and Blood Vessels
   a. Right heart failure from any cause
   b. Pericarditis, acute and chronic
   c. Thrombosis or obstruction of hepatic veins, or of the inferior vena cava above the level of entry of the hepatic veins
2. Diseases of the Liver and Portal Venous System
   a. Cirrhosis
   b. Syphilis of the liver
   c. Yellow atrophy and hepatitis
   d. Thrombosis or obstruction of portal or splenic vein, or hepatic artery
   e. Arteriovenous aneurysm involving the hepato-portal, or splenic vessels (Cassel *et al.*[7])
3. Diseases of the Peritoneum
   a. Tuberculous peritonitis
   b. Simple peritonitis, acute and chronic
   c. Neoplasm: primary and metastatic, involving peritoneum
   d. Hydatid disease
4. Female Reproductive Organ Diseases
   a. Malignant tumors
   b. Benign tumors, cystadenomas and fibromas
   c. Endometriosis (Charles[9])
5. Diseases of the Kidney
   a. As part of generalized anasarca in the nephrotic syndrome
   b. Associated with fluid retention in oliguria or anuria caused by primary renal disease
6. Diseases of the Blood and Lymphatic System
   a. Severe anemia
   b. Leukemia
   c. Lymphomas
   d. Obstruction of lymphatic channels draining intestinal tract by neoplasm, parasites, and others.
7. Nutritional Deficiency States or Wasting Disease with Hypoproteinemia and Avitaminosis
8. Endocrine Diseases
   a. Myxedema
   b. Hyperadrenalism
   c. With increased antidiuretic hormone? (Rowntree *et al.*[51])
9. Traumatic and Acute Causes
   a. Rupture of a hollow viscus: stomach, intestine, bladder, gallbladder
   b. Ruptured tubal pregnancy or ovarian follicle
   c. Rupture of abdominal aneurysm or spleen
   d. Ruptured cysts of peritoneum, kidney, liver, or pancreas
   e. Intestinal obstruction
   f. Acute pancreatitis

10. Iatrogenic Disease: Overloading with Fluid and Electrolytes
11. Diseases of Unknown Etiology
    a. Collagen diseases: disseminated lupus erythematosus, rheumatic fever
    b. "Multiple serositis"
    c. "Benign transitory ascites" (Todd[58])

The present analysis is centered primarily about the disease groups cirrhosis (47 cases), congestive heart failure (24 cases), neoplasm (53 cases), and tuberculosis of the peritoneum (14 cases). The other less common causes occurred in too few numbers to render statistical study possible; hence, several of these will be alluded to briefly at the end of the discussion. Renal disease, which ordinarily is a relatively frequent cause of ascites, was found in only one case in the present series and therefore will be included in the latter group.

Results. In this section primarily the four common causes of ascites will be dealt with.

BLOOD DETERMINATIONS. *Bromsulphalein Dye Retention.* This test was performed 32 times on 24 cases of ascites due to cirrhosis, and dye retention was abnormally high in all cases, ranging from 6.5% to 55% (considering 5% or below as the normal range). Three cases did fall, however, into the 6 to 10% range which is near normal.

The test was frequently abnormal in other diseases; dye retention was increased in all cases of congestive failure in which the test was done, and in 4 of 6 cases of neoplasm. The probable reasons for these abnormal tests were passive congestion and hypoxia of the liver with the resulting hepatocellular impairment in heart failure, and liver metastases with parenchymal replacement in neoplastic disease.

Israel and Reinhold[26] found that of 21 cases of cirrhosis with ascites, 19 exhibited abnormal BSP retention; of the two that had normal retention, one had an abnormal test at a later date. Greene *et al.*[18] observed prolonged dye retention in 30 of 31 cases.

Studies on congestive heart failure (Chavez, Sepulveda and Ortega[10], Evans *et al.*[12], Felder, Mund and Parker[13]) have shown that BSP retention is abnormal in from 85 to 100% of cases (the presence of ascites was not noted in these reports), but tends to return to normal with compensation, except in those cases manifesting persistent hepatomegaly at dry weight (Layne, Schemm and Hurst[34]). The test was almost uniformly abnormal when the dye was used in quantities of 5 mg. per kg. body weight and when 45-minute specimens were obtained. Other quantities appeared to give less sensitive results. The present series suggests that the percentage of cases showing abnormal retention will be maximum in congestive failure complicated by ascites.

Serum Proteins. Serum albumin levels were found to be uniformly low in both cirrhosis and neoplasm with ascites, being rarely as high as 4 gm.% in either disease. In only one of 102 determinations on cirrhotics, and in none of 37 on neoplasm cases, did the albumin exceed this level. On the other hand, the level more often exceeded 4 gm.% in congestive heart failure and tuberculosis.

Inversion of the albumin-globulin ratio was common in cirrhosis, but on at least one occasion in 13 of 47 cases, it was not inverted. The ratio was also commonly inverted in other conditions, and was, therefore, of little value as a practical aid in diagnosis.

Total serum globulin values appear to be of some help in differential diagnosis since the level in cirrhotics was above 4.1 gm.% in 25.5% of all determinations while in other conditions it

exceeded this critical level in only one case.

The electrophoretic pattern of the globulin fraction may be of more diagnostic assistance, for it has been found (Kay[29], Rovelstad[50]) that alpha-globulin is commonly elevated in carcinoma involving the peritoneum, as opposed to a frequent elevation of gamma-globulin in cirrhosis; other conditions have produced less clear results.

ASCITIC FLUID STUDIES. *Color and Appearance.* It has been noted in the past that grossly bloody fluid is found with the greatest frequency in peritoneal effusions due to malignancy. In the present study, however, the incidence of gross blood was rather low, occurring in only 15 of 58 fluid specimens caused by malignant neoplasms. It should be noted also that its occurrence by no means excludes other diseases since, in 2 of 63 specimens from cirrhotics, and, in 2 of 23 from cases with heart failure, gross blood was found. In the 2 cirrhotics, however, this happened only when a second tap was done. That uncomplicated cirrhosis can cause the formation of hemorrhagic peritoneal fluid even on an original tap has been noted previously (Mandel and Remenchik[40]). It has been suggested that this may be due to the usual low prothrombin levels, or platelet deficiencies as seen when hypersplenism is present, or both. It is difficult to account for the presence of bloody fluid in the 2 cases of congestive heart failure, for one of these was a specimen obtained by first tap; mechanical trauma during paracentesis cannot be excluded as a possible cause.

The finding of a milky-appearing fluid is important and will be discussed at greater length below.

Another observation which seems to have slight value in differential diagnosis is the presence of a green hue to the fluid. This was observed occasionally in neoplasm (5 of 58 specimens) and congestive failure (3 of 23), but was absent in 63 fluids from cirrhotics. This green color is due possibly to the breakdown of blood pigment, thus explaining its presence in malignancy.

A viscoid or mucoid appearance and consistency may signify the presence of metastatic colloid carcinoma (Jeter, Epps and Hart[27]) or pseudomyxoma peritonei: one of the latter was observed in the present series.

Specific Gravity. This test possibly could be of greater value if we were cognizant of its relatively large variation with temperature change. The value at room temperature may be as much as 0.005 higher than at body temperature. These figures are given for water, but ascitic fluid, like water, expands almost identically with heat (Weech, Reeves and Goettsch[63]). It will be assumed that this variable was at least partially eliminated in this study since the fluids probably were tested at room temperature in almost all instances. Another potential source of error is failure to correct for variations among hydrometers. The correction factor for each instrument is determined by obtaining readings on distilled water, a known substance, at the temperature for which the instrument is calibrated (usually 15° C.). Still another difficulty in reading arises from the action of surface tension on the protruding stem. Even under the best of conditions, the hydrometer method is said to have an accuracy of plus or minus 0.001 (Hidnert and Peffer[21a]).

The author found that, in cirrhosis and congestive heart failure, a specific gravity of over 1.016 was quite rare, occurring in only 2 of 37 fluids from the former and in none of 23 from the latter. In neoplasm, the specific gravity

ranged widely, varying from 1.004 to 1.023, with an average of 1.0125. In tuberculous peritonitis, the figure tended to be above 1.016.

Earlier reports (Foord, Youngberg and Witmore[14], Miller[42], Paddock[45], Phillips and McDonald[49], Rovelstad *et al.*[50], Runeberg[52]) for the most part, corroborate the present data except in one respect: Ascitic fluids caused by congestive heart failure have been frequently reported to have a specific gravity greater than 1.016. This disparity probably reflects the unreliability of specific gravity rather than any basic disagreement. The average specific gravity for this condition in the present series of cases (1.012), however, is in fairly close agreement with the results of others.

Ascitic Fluid Proteins. In the present study, total protein values for ascitic fluid were slightly more diagnostic than were specific gravities. Differences between the two can be attributed mainly to the inaccuracies, as outlined previously, of specific gravity determination rather than to any innate superiority of protein determinations. It is generally conceded that both tests have similar significance; and, if carefully controlled studies are undertaken, one can calculate with a relatively high degree of accuracy, in most cases, the protein values from the specific gravity of a serous fluid (Paddock[46], Weech, Reeves and Goettsch[63]). This is not surprising since smaller diffusible molecules which also may alter the specific gravity of a serous fluid tend to be present in concentrations equaling blood values and, therefore, remain relatively constant. Occasional exceptions, however, such as uremia and severe jaundice would tend to cause aberrations of the specific gravity, further diminishing its accuracy as compared to protein content.

The present data suggest that ascitic fluid protein values depend not only upon the disease process responsible, but upon the level of serum proteins as well; a roughly positive correlation between serum albumin and ascitic fluid protein levels was found, both among all cases taken collectively, and among the cases within each disease category (see Fig. 1).

The present findings were as follows: all 38 fluids tested from cirrhotics contained 2.5 gm.% protein or below. All 7 fluids from tuberculous peritonitis contained 3.3 gm.% or above. Neoplasm and congestive failure caused the formation of fluids which contained a wide variation of protein, the former ranging from 0.90 to 5.6 gm.% and the latter, from 1.3 to 4.1 gm.%.

The relatively high average protein concentration in ascitic fluid caused by congestive heart failure is worthy of special comment; in 6 of 16 such specimens tested, the total protein level was above 3.0 gm.%. This finding has been pointed out previously by Paddock[45], who noted that cardiac ascites frequently contained relatively higher concentrations of protein than one usually expects with mechanical effusion, tending to parallel the high specific gravity which he also observed to be over 1.016 in about one-third of these cases. This surprisingly high average protein concentration probably can be explained on the basis of 1) higher serum albumin values in this disease, 2) vascular anoxia, causing increased capillary permeability, and 3) ease of therapeutic diuresis of water and electrolytes from the body, causing a diminution of fluid in the peritoneal cavity without a corresponding reduction of protein in this compartment.

Extensive studies of the protein fractions in serous effusions are lacking. However, most available evidence indicates that, in general, serous fluids contain all fractions of protein in

roughly similar proportions to those present in the coexisting plasma (Keller and Spang[30], Luetscher[37], Myers and Keefer[43], Paul *et al.*[47], Rovelstad et *al.*[50], Vannini and Ippolito [60,61] Whitman, Rossmiller and Lewis[64]). The exact protein fraction concentrations in ascitic fluid depend upon three factors: 1) the nature of the underlying disease, 2) the concentration of the fractions in the corresponding plasma, and 3) the relative size of the various molecules. In nephrosis, cirrhosis, and congestive heart failure, albumin, which is the smallest of the molecules, is present in the fluid in greater proportions than in the plasma. Gamma-globulin, which is next smallest in size, also frequently is present in the fluid in increased proportions, but not as often or to as great an extent as albumin. The remaining larger molecular fractions are generally present but in smaller percentages than seen in the corresponding plasma. While ascitic fluid in these above three conditions contains this proportional arrangement of protein fractions, congestive heart failure tends to produce all components in greater absolute quantities. Cancer is capable of forming fluid containing, in many instances, large absolute amounts of all fractions, especially albumin and gamma-globulin; but in this condition, unlike those described above, the latter two fractions occasionally show inordinate increases in concentration, sometimes exceeding those seen in the homologous sera (Rovelstad *et al.*[50]). Tuberculous effusions are not clearly characterized, and some evidence indicates that they may vary with age (Vannini and Ippolito[61]); earlier effusions tend to contain a pre-

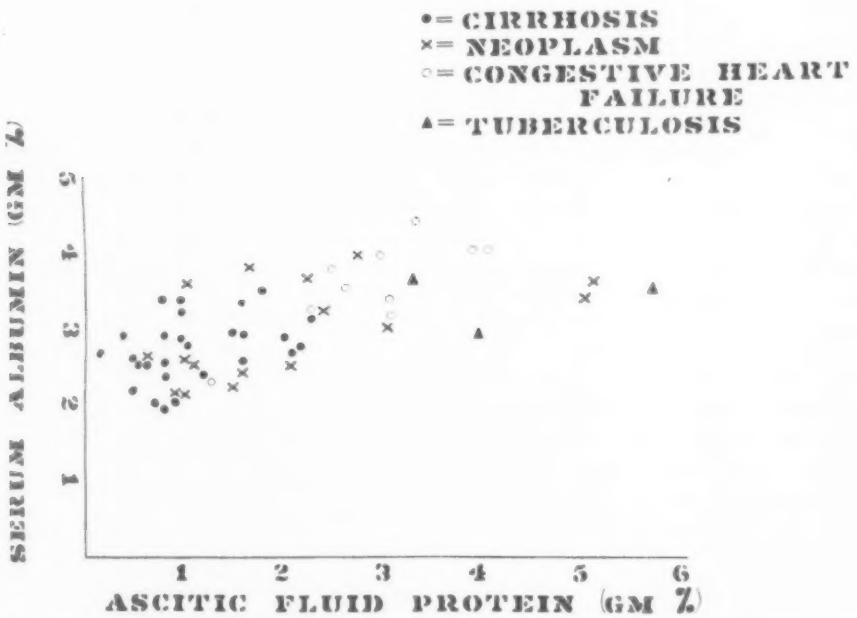


Fig. 1.—Graph showing the roughly positive correlation between serum albumin and ascitic fluid protein

dominance of albumin and alpha-1-globulin with little change in gamma-globulin while effusions of long standing show a tendency toward relatively low albumin and alpha-1-globulin with high gamma-globulin values. The results in tuberculous and neoplastic effusions, if proven valid, are not easily explained; one would be required to postulate a theory encompassing more than mere mechanical passage of the smaller molecules in predominating numbers from the plasma into the peritoneum.

At the present time, practical application of these observations on protein fractions is limited to the differential diagnosis between carcinoma and cirrhosis. Rovelstad *et al.*[50] have shown recently that, by measuring albumin and gamma-globulin levels of simultaneously obtained ascitic fluid and serum, and by calculating their respective fluid serum ratios, they could largely separate the cirrhotic patients from those with malignancy. They found that 85% of 39 cancer patients had an ascitic fluid albumin/serum ratio of greater than 0.462 while in all 24 cirrhotics the ratio fell below this figure. They found also that 68% of 22 cirrhotics had a fluid gamma-globulin/serum gamma-globulin ratio of less than 0.167 while in all of 39 cancer patients it was above this level. Further data are awaited which will characterize these and other conditions more clearly.

Analyzing the above data, one may wonder why it is common practice to divide ascitic fluids into two large groups, depending upon whether each individual value of total protein or specific gravity, or both, is above or below an arbitrary dividing line. It is generally held that fluids containing more than 3.00 gm.% protein and above 1.016 specific gravity are termed "exudates," and those below this dividing line are designated "transudates." Moreover, "exudate" usually denotes that which is due to inflammation, and "transudate" signifies a hydrostatic or osmotic etiology; the two terms generally are considered to be mutually exclusive. It is the author's opinion that, in view of the present data, this present usage, if applied to peritoneal fluid, can potentially result in erroneous conclusions, for many believe that effusions due to such diseases as congestive heart failure (caused by hydrostasis) and carcinoma (presumably caused by multiple factors) can be placed into separate categories. In reality, these diseases cause effusions of varying levels of protein and specific gravity, and each is capable of occupying either category. It would appear to be more logical to discard this terminology entirely when discussing ascites in favor of understanding the disease groups separately and taking into account the level of serum proteins in each individual case. Another approach is to measure the ratio between simultaneously obtained serum and ascitic fluid proteins (especially albumin) and to correlate this ratio with etiology as suggested by Rovelstad *et al.* This method would be analogous to that of Seidel[54], who measured the total nitrogen ratio between these two media and obtained what also appear to be slightly more diagnostic results than those achieved by most studies on ascitic fluid protein alone. In a study of 220 cases, he found that in hypoproteinemia, this ratio averaged 6.33 (range, 5.2 to 14.8); in cirrhosis, 4.10 (2.0 to 5.6); in congestive failure, 2.08 (1.9 to 3.6); in carcinoma, 1.58 (1.0 to 2.4); and in tuberculosis, 1.44 (1.3 to 1.6).

Cell Count. Red blood cell counts are of little value except to substantiate the finding of a grossly bloody fluid. in which case it will be higher usually

than 10,000 RBC per ml. Lower red blood counts were encountered in a variety of fluids and were, therefore, not helpful in diagnosis.

In mechanical effusions due to noninfectious causes, the predominant cells seen in the sediment are usually large mononuclear mesothelial cells shed from the peritoneal surface. The total number of cells (RBC excluded) seldom exceeded 2,000.

It is generally held that large numbers of lymphocytes frequently occur in the ascitic fluid of tuberculous peritonitis. In most other types of bacterial peritonitis, neutrophils usually predominate and may contain bacteria engulfed within their cytoplasm, although these organisms also may be found free in the fluid (Steinberg[55]). The number of such cases in this series was too small to draw any conclusions concerning this.

Eosinophils are seen most commonly in hemorrhagic effusions (Paddock[45]), hydatid disease (Aubrey and Thiodet[4]), and when repeated aspirations are made (Foord, Youngberg and Witmore[14]).

Cytologic Diagnosis. Certainly our most valuable current diagnostic procedure performed upon peritoneal fluid is the examination for malignant cells. The diagnosis of malignancy by this means, however, is extremely difficult to make, for in many instances the mesothelial cells normally found in peritoneal fluid may simulate malignant cells very closely. This is especially true when these cells have undergone metaplasia from inflammatory causes; even the most experienced observer may be tempted to call these cells "malignant" (Foot[16]). As a result, most pathologists have adopted a conservative viewpoint in interpretation, reserving a report of "positive" only for fairly obvious malignant cells, thus insuring a high degree of accuracy with a positive report. A report of "negative" always has been considered unsatisfactory as a means of ruling out malignancy.

A review of cellular morphology is beyond the purview of this paper; hence, for a thorough discussion of cytology, the reader is referred to several excellent studies in which the various techniques are presented and compared (Foot[15,16], Goldman[17], Luse and Reagan[38], Saphir[53], Zemansky[66]).

TABLE 3.—RESULTS OF THE CYTOLOGIC STUDIES FOR MALIGNANCY IN THE VARIOUS DISEASES

	Specimens Positive	*Specimens Negative*
Malignancy	24	7
Cirrhosis	1	33
Congestive heart failure	0	11
Tuberculosis	0	9
Miscellaneous benign causes	0	6
Total no. Specimens {Malignant	24	7
Total no. Specimens {Benign	1	59

In the present series (Table 3), both the cytologic smear and cell block techniques were used; the present number was too small to allow a comparison of the results of the procedures. Both methods have been reported to yield approximately the same results although they are said to complement each other in many instances (Foot[16]). Ideally, each fluid should be subjected to both procedures for optimum results. Of 31 specimens from patients with malignant disease, 24 (77%) were reported as positive for malignant cells. This percentage coincides roughly with that of most reports (which range from 45 to 80%) (Chapman and Whalen[8], Goldman[17], Honigman[24], Jeter, Epps and Hart[27], Lewin[35], Luse and Reagan[38], Phillips and McDonald[49], Zemansky[66]).

In the present study, only one positive report was found among 60 fluid

specimens caused by benign diseases. This low rate (1.7%) is fairly good evidence of a conservative approach to interpretation and compares favorably with that of other reports: 21 (51.1%) of 408 cases found in the literature (effusions in all areas included) were interpreted falsely as positive (Chapman and Whalen[8], Foot[16], Helwig[21], Honigman[24], Jeter, Epps and Hart[27], Phillips and McDonald[49]).

TABLE 4.—OCCURRENCE OF POSITIVE CYTOLOGIC REPORTS IN THE VARIOUS PRIMARY SITES OF MALIGNANCY

Primary Site of Malignancy	*No. Cases*	*Positive Specimens*	*Negative Specimens*
Ovary	5	5	0
Endometrium	3	4	0
Pancreas	4	1	3
Stomach	3	3	0
Cervix	2	2	1
Large Bowel	2	1	1
Kidney	1	1	0
Adrenal	1	1	0
Liver	1	0	1
Gallbladder	1	1	0
Breast	1	1	0
Bronchus	1	0	1
Reticulum cell sarcoma	1	1	0
Site undetermined	3	3	0
Totals		24	7

Various types of neoplasm have been found to show differing propensities toward shedding cells into the peritoneal fluid. In a large series in which both peritoneal and pleural fluids were studied, Luse and Reagan[38] found that ovarian malignancies gave the highest rate of recovery (94%), while tumors of the lymphoma group tended to give the lowest yields (46%); other tumors approached the mean more closely. In the present study (Table 4), ovarian malignancies gave the highest yield (5 of 5), and carcinoma of the pancreas, the most false negatives (3 of 4). Only one specimen due to lymphoma was examined and was found to be positive.

Repeated taps are emphasized as a means of increasing the rate of positive yields in cases of malignancy (Foot[16], Honigman[24], Jeter, Epps and Hart[27]). One case was observed (epidermoid carcinoma of the cervix) in which, after a negative initial tap, the second specimen was reported as positive.

It has been stated that, from the cytologic picture alone, one can predict the primary site of the neoplasm in many instances (Foot[15], Perou and Littman[48], Zemansky[66]); well differentiated tumor cells, mesotheliomas, and certain types of sarcoma such as reticulum cell sarcoma, Hodgkin's sarcoma, and to a lesser degree, lymphosarcoma lend themselves to such analysis. Undifferentiated cells are of little aid in the localization of the primary site.

It has been stressed also previously that when malignant cells are found in the ascitic fluid, peritoneal seeding is present, and the prognosis for cure is extremely grave (Foot[16], Helwig[21], Honigman[24]). The only possible exceptions to this rule might be an occasional ovarian neoplasm and rare primary mesothelioma, where peritoneal seeding conceivably could be absent, and yet where one could find neoplastic cells in the fluid.

Chylous Ascites. Free chyle in the peritoneum gives the ascitic fluid a grossly bluish-white, milky, or creamy appearance due to the presence of a large amount of fat normally present in chyle. After standing, the fluid will contain a lipid layer on its surface. If fat is eliminated from the diet, the creamy color will rapidly clear, leaving a plasma-like appearance within 24 hours (Whittlesey, Ingram and Riker[65]). Other characteristics of this

fluid are as follows (Hoffman[22]): 1) The specific gravity varies around 1.020. 2) Microscopic examination reveals many fat globules (which stain positively with Sudan III) and occasionally lymphocytes, but only rarely are neutrophils or red blood cells present. 3) Chemically, the fluid is alkaline in reaction and can be coagulated by the addition of nitric acid but not by heat. Shaking with ether after the addition of alkaline solution causes the fluid to become clear (Todd, Sanford and Wells[57a]). Total fat determinations tend to reveal a content of 0.5 gm.% or more, but these levels correlate only roughly with the gross appearance of the effusion (Rovelstad *et al.*[50]).

The pathogenesis of this condition is leakage of the lymphatic channels which drain the intestine, a situation which may arise as a result of obstruction or trauma. Lesions may be congenital or acquired and located at any point of lymphatic drainage from the peripheral lacteals to the thoracic duct centrally. Causes for chylous ascites are listed as follows (Hoffman[22,23], Whittlesey, Ingram and Riker[65]):

1. Enlargement of mediastinal nodes by tuberculosis
2. New growths in the mediastinum or abdomen
3. Filariasis and bilharziasis
4. Trauma of thorax or abdomen
5. Surgical injury to thoracic duct or cysterna chyli
6. Congenital maldevelopment of central or peripheral lymphatics with stenosis or atresia
7. Thrombosis of innominate or left subclavian vein with resultant obstruction of the thoracic duct.

Chyloperitoneum is also occasionally seen in association with an acute abdomen: Hoffman[22] found that free chyle may be associated with local obstructive lesions such as strangulated hernia, volvulus, and appendicitis, but he also found several instances of chyle in an acute abdomen in which no demonstrable lesion could be found. He postulated that rupture of lacteals will occasionally occur in a normal individual after a fatty meal and will result in the outpouring of chyle, an irritating substance, into the peritoneal cavity, thus simulating an acute surgical abdomen.

Listed in the present series are 3 cases which proved to be chylous ascites: one in conjunction with an acute abdomen with no demonstrable cause, as in the idiopathic cases described by Hoffman; one associated with giant follicular lymphoblastoma; and a third with an unclassified lymphoma. In fluid specimens from all 3 cases, fat was readily identified microscopically, and, in the 2 tested for protein, the content was greater than 3 gm.%. Fluids from 3 additional cases were described as "milky," but no further testing was done. This latter group was composed of a case of lymphosarcoma, one of carcinoma of the pancreas, and one of congestive failure.

Conditions which give rise to high blood lipid levels may also impart an opalescent milky appearance to the ascitic fluid. This was observed in the one case of the nephrotic syndrome caused by chronic glomerulonephritis.

Since the majority of chylous effusions occur in malignancies, some workers (Rovelstad *et al.*[50]) have found that the measurement of total fat in ascitic fluid can aid in separating the cancer and cirrhosis groups. They found that cancerous effusions frequently showed elevation of total fat content above a critical level of 0.35 gm.% (the majority of these fluids were grossly clear), while cirrhotics all fell below this level.

LESS COMMON CAUSES OF ASCITES. Ascites in conjunction with other dis-

eases occurs so infrequently that it is extremely difficult to glean from the literature sufficient laboratory data to render statistical analysis meaningful. The explanation for this inadequacy lies not only in the rarity of these diseases, but also in the fact that ascites is neither an early nor a prominent feature in many of these conditions, and the study of characteristics of the fluid has thus little practical value. Nonetheless, there are several points which are worth bearing in mind.

Renal Disease. The present series includes only one case of ascites due to renal disease: chronic glomerulonephritis with the nephrotic syndrome. Ascitic fluids were examined on 4 separate occasions and were found to contain very little protein and few cells. This agrees with the findings of others. Ascitic fluid seen in nephrosis generally is found to have a specific gravity below 1.013 and less than 1.5 gm.% protein (Miller[42], Paddock[45], Weech, Reeves and Goettsch[63]).

Myxedema. This disease may be associated with protein-rich peritoneal effusions which are capable of forming even in the absence of congestive heart failure, an occasional concomitant feature of myxedema (Madenberg, Byfield and Baker[39]). In 6 reported cases where testing was done, the ascitic fluid contained 2.2 to 5.2 gm.% protein (average, 3.6) (Hanssen[19], Madenberg, Byfield and Baker[39], Tanaka and Clifford[56]). A high protein content is also characteristic of other effusions occurring in myxedema and probably is a reflection of the generally increased capillary permeability which may be seen in this disease (Lange[32]). Rarely, ascites may be a prominent and almost the sole sign of myxedema (Laroche and Rapin[33], Madenberg, Byfield and Baker[39], Tracey and Donovan[59]), necessitating repeated paracenteses for relief in some instances.

Systemic Lupus Erythematosus. This and other collagen diseases have been indicated as the cause of multiple effusions, including ascites. Peritoneal effusion occurs in a relatively small proportion of patients with lupus but is not listed as an early sign in this disease (Harvey *et al.*[20]). When present it is usually scanty and easily overlooked (Armas-Cruz *et al.*[2]). While this manifestation has been reported to occur with as high a frequency as 24% of 62 cases in Dubois'[11] series, it was present only when either congestive failure or nephropathy was present. Thus, one would be led to infer that, despite the frequent finding of polyserositis in systemic lupus erythematosus, actual fluid found clinically in the peritoneum would generally have the characteristics of a mechanical effusion, paralleling that found in renal and heart disease.

Hepatic Vein Thrombosis (Budd-Chiari Syndrome). Although this disease is only rarely seen, when it does occur clinically, ascites is an almost invariable feature, appearing in approximately 95% of cases (Thompson[57]). Experiments with dogs have shown that obstruction of the vena cava above the entering hepatic veins results in ascites of high specific gravity and protein values (Volwiler, Bollman and Grindley[62]), but this apparently is not generally the case in humans, for upon perusal of the literature, it was found that in 7 of the reported cases where these values were mentioned (Armstrong and Carnes[3], Hsiang Len Tseng[25], Kelsey and Comfort[31], Kibel and Marsden[31a], Little and Montgomery[36], Norris[44], Thompson[57], Massachusetts General Hospital[67]), the specific gravity ranged between 1.008 and 1.017 (average 1.013), and 6 cases showed a protein variation of 1.0 to 4.0 gm.% (2.25 gm.%). The explanation for these relatively low specific gravity and protein values in humans may lie

in the fact that there was a tendency toward hypoproteinemia as the disease progressed, and by the time paracentesis was done, the fluid already may have reflected this change in the blood. Bromsulphalein dye retention was consistently elevated when mentioned, tending to be near normal early and to show a progressive rise with time.

Portal Vein Thrombosis. In contrast to hepatic vein or vena cava thrombosis, obstruction of the portal vein *per se* usually does not result in ascites (Baggenstoss and Wollaeger[5], Volwiler, Bollman and Grindley[62]). There is evidence that isolated portal obstruction may cause ascites in humans, but most cases of portal thrombosis exist secondarily to other conditions which in themselves cause ascites (cirrhosis, neoplasm, and others). Baggenstoss and Wollaeger[5] reported that, of 215 cases of portal thrombosis reviewed at the Mayo Clinic, only 15 were free of other potential causes of ascites, and only 5 of the latter were associated with ascites. Very few data, therefore, are available on the laboratory findings in isolated portal thrombosis associated with ascites.

In the present series, 3 cases of portal thrombosis were found: 2 were associated with malignant disease, and a third with cirrhosis. These cases are listed within their respective primary disease categories; the results of the studies obtained were in no way distinctive.

Hydatid Disease (Echinococcosis). This disease, uncommon in the U.S.A., is believed capable of causing ascites by three means (Aubrey and Thiodet[4]): 1) portal vascular compression by an expanding cyst, 2) cirrhosis of the liver secondary to parenchymal replacement or hepatic vein obstruction, and 3) local allergic reaction of the peritoneum. The peritoneal fluid is generally clear yellow in color and of low protein content. Smears of the fluid reveal an abundance of eosinophils in many cases. If one inadvertently withdraws contents from within a cyst, the fluid procured will be crystal clear with a specific gravity of 1.007 to 1.015; scolices and hooklets may be found on microscopic examination of the sediment (Jidejian[28]).

Summary and Conclusions. From a review of 142 cases manifesting the sign ascites and from previous investigation by others, the following conclusions are drawn concerning patients with ascites:

1. Bromsulphalein dye retention is almost always abnormal in both cirrhosis and congestive heart failure with ascites. Malignancy may or may not give prolonged dye retention.

2. Hypoalbuminemia below 4 gm.% is common in all conditions associated with ascites, being most marked in renal disease, cirrhosis, and neoplastic disease.

Total serum globulin levels tend to run higher in cirrhosis than in the other conditions.

It has been cited that in cirrhosis with ascites, serum protein electrophoresis frequently shows an increase in gamma-globulin fraction; whereas, in malignancy with ascites, the alpha-globulin commonly is elevated.

3. The appearance of the ascitic fluid is grossly bloody in about one-fourth of all neoplastic effusions. Other conditions occasionally produce gross blood, but this usually is found after at least one previous tap has been done.

4. Protein content and specific gravity of the ascitic fluid are roughly proportional to each other; probably due to inaccuracies of the latter, protein determinations appear to yield slightly more reliable results. In cirrhosis and renal disease, the total protein is almost always below 3 gm.% (and gen-

erally below 1.016 specific gravity), but these values frequently are above this level in congestive failure. Both total protein and specific gravity range widely in neoplastic disease, and both are high in tuberculosis of the peritoneum.

5. Ascitic fluid protein depends not only upon the responsible disease but upon the level of serum albumin as well; hence, one must take both factors into account when interpreting fluid values. It has been suggested that measurement of serum: ascitic fluid protein (or albumin) ratio may be of more diagnostic aid than the ascitic fluid protein valué alone.

Few studies on ascitic fluid protein electrophoretic pattern have been made; the results are summarized.

6. Cell counts are of some value in substantiating the presence of gross blood in the fluid; these fluids are apt to contain greater than 10,000 red blood cells per ml. Other findings occasionally may be of aid and these were discussed briefly.

7. Cytologic studies for malignancy are found to be positive in about three-fourths of the specimens from malignant disease. Sundry primary sites tend to yield varying percentages of positive results. False positive reports are rare.

8. Chylous ascites occurs as a result of damage or obstruction of lymphatic drainage of the bowel. In the present study it was seen most frequently in neoplastic disease.

9. Several rarer causes for ascites are discussed briefly.

ACKNOWLEDGMENTS: I am indebted to David Rosenbaum, M.D., Chief of Pathology, Indianapolis Veterans Administration Hospital, and William Weiss, M.D., Chief of Pulmonary Diseases, Philadelphia General Hospital, for aid and encouragement in the preparation of this paper. I also wish to thank those of Indianapolis Veterans and General Hospitals and the Indiana University Medical Center for their excellent cooperation in supplying the necessary material.

REFERENCES

1. Abrahams, A.: French's Index of Differential Diagnosis. Baltimore: The Williams & Wilkins Co., p. 79, 1954.
2. Armas-Cruz, R., **Harnecker, J., Ducach, G., Jalil, J.,** and **Gonzalez, F.**: Am. J. Med., **25**, 409, 1958.
3. **Armstrong, C. D.,** and **Carnes, W. H.**: Am. J. Med. Sci., **208**, 470, 1944.
4. **Aubrey, G.,** and **Thiodet, J.**: Algerie Med., **59**, 171, 1955.
5. **Baggenstoss, A. H.,** and **Wollaeger, E. E.**: Am. J. Med., **21**, 16, 1956.
6. **Cabot, R. C.**: Am. J. Med. Sci., **143**, 1, 1912.
7. **Cassel, W. G., Spittel, J. A., Ellis, F. H.,** and **Bruwer, A. J.**: Circulation, **16**, 1077, 1957.
8. **Chapman, C. B.,** and **Whalen, E. J.**: New England J. Med., **237**, 215, 1947.
9. **Charles, D.**: Obst. & Gyn., New York, **10**, 309, 1957.
10. **Chavez, E., Sepulveda, B.,** and **Ortega, I.**: J. Am. Med. Assn., **121**, 1276, 1943.
11. **Dubois, E. L.**: Ann. Int. Med., **38**, 1265, 1953.
12. **Evans, J. M., Zimmerman, H. J., Wilmer, J. G., Thomas, L. J.,** and **Ethridge, C. B.**: Am. J. Med., **13**, 704, 1952.
13. **Felder, L., Mund, A.,** and **Parker, J. G.**: Circulation, **2**, 286, 1950.
14. **Foord, A. G., Youngberg, G. H.,** and **Witmore, V.**: J. Lab. & Clin. Med., **14**, 417, 1929.
15. **Foot, N. C.**: Am. J. Path., **30**, 661, 1954.
16. Idem: Ibid., **32**, 961, 1956.
17. **Goldman, A.**: Arch. Surg., **19**, 1672, 1929.
18. **Greene, C. H., McVicar, C. S., Snell, A. N.,** and **Rowntree, L. G.**: Arch. Int. Med., **40**, 159, 1927.

19. **Hanssen, P.:** Acta med. Scandinav., **90**, 277, 1938.
20. **Harvey, A. M., Shulman, L. E., Tumulty, P. A., Conley, C. L.,** and **Schoenrich, E. M.:** Medicine, **33**, 291, 1954.
21. **Helwig, E. B.:** J. Missouri Med. Assn., **39**, 73, 1942.
21a. **Hidnert, P.,** and **Peffer, E. L.:** Density of Solids and Liquids, Washington: National Bureau of Standards, 1950.
22. **Hoffman, W.:** Internat. Abstr. Surg., **98**, 209, 1954.
23. Idem: New York State J. Med., **57**, 1611, 1957.
24. **Honigman, A. N.:** Surg. Gyn. & Obst., **81**, 295, 1945.
25. **Hsiang Len Tseng:** A.M.A. Arch. Path., **60**, 319, 1955.
26. **Israel, H. L.,** and **Reinhold, J. G.:** J. Lab. & Clin. Med., **23**, 588, 1938.
27. **Jeter, H., Epps, C.,** and **Hart, M. S.:** South. Med. J., **35**, 519, 1942.
28. **Jidejian, Y.:** Surgery, **34**, 155, 1953.
29. **Kay, H. E. M.:** Brit. Med. J., **2**, 1025, 1954.
30. **Keller, C.,** and **Spang, K.:** Deutsch. Arch. klin. Med., **200**, 155, 1953.
31. **Kelsey, M. P.,** and **Comfort, M. W.:** Arch. Int. Med., **75**, 175, 1945.
31a. **Kibel, M. A.,** and **Marsden, H. B.:** Arch. Dis. Child., **31**, 225, 1956.
32. **Lange, K.:** Am. J. Med. Sci., **208**, 5, 1944.
33. **Laroche, C.,** and **Rapin, M.:** Ann. Endocrinol., **14**, 245, 1953.
34. **Layne, J. A., Schemm, F. R.,** and **Hurst, W. W.:** Gastroenterology, **16**, 91, 1950.
35. **Lewin, E.:** Zbl. Gynäk., **75**, 489, 1953.
36. **Little, R. D.,** and **Montgomery, P.O'B.:** Ann. Int. Med., **37**, 197, 1952.
37. **Luetscher, J. A.:** J. Clin. Invest., **20**, 99, 1941.
38. **Luse, S. A.,** and **Reagan, J. W.:** Cancer, **7**, 1167, 1954.
39. **Madenberg, F., Byfield, G. V.,** and **Baker, L. A.:** A.M.A. Arch. Int. Med., **93**, 787, 1954.
40. **Mandel, W.,** and **Remenchik, A.:** Gastroenterology, **27**, 231, 1954.
41. **Mensh, M.,** and **Banks, R.:** *Gastroenterology*, edited by **Bockus, H. L.**, Philadelphia: W. B. Saunders Co., pp. 207–23, 1946.
42. **Miller, J. L.:** Am. Med., **8**, 835, 1904.
43. **Myers, W. K.,** and **Keefer, C. S.:** Arch. Int. Med., **55**, 349, 1935.
44. **Norris, T. S.:** Lancet, **1**, 232, 1956.
45. **Paddock, F. K.:** New England J. Med., **223**, 1010, 1940.
46. Idem.: Am. J. Med. Sci., **201**, 569, 1941.
47. **Paul, W. D., Gordon, J. D., Dryer, R. L.,** and **Routh, J. I.:** Fed. Proc., **8**, 235, 1949.
48. **Perou, M. L.,** and **Littman, M. S.:** Am. J. Clin. Path., **25**, 467, 1955.
49. **Phillips, S. K.,** and **McDonald, J. R.:** Am. J. Med. Sci., **216**, 121, 1948.
50. **Rovelstad, R. A., Bartholomew, L. G., Cain, J. C., McKenzie, B. F.,** and **Soule, H. H.:** Gastroenterology, **34**, 436, 1958.
51. **Rowntree, L. G., Winter, W. J., Brown, H. E.,** and **Boucek, R. J.:** J. Am. Med. Assn., **168**, 411, 1958.
52. **Runeberg, J. W.:** Deutsch. Arch. klin. Med., **35**, 266, 1884.
53. **Saphir, O.:** Am. J. Clin. Path., **19**, 309, 1949.
54. **Seidel, K.:** Deutsche med. Wchnschr., **79**, 1089, 1954.
55. **Steinberg, B.:** J. Am. Med. Assn., **116**, 572, 1941.
56. **Tanaka, K. R.,** and **Clifford, G. O.:** New England J. Med., **258**, 7, 1958.
57. **Thompson, R. B.:** Arch. Int. Med., **80**, 602, 1947.
57a. **Todd, J. C., Sanford, A. H.,** and **Wells, B. B.:** Clinical Diagnosis by Laboratory Methods, Philadelphia: W. B. Saunders Co., p. 624, 1953.
58. **Todd, J. W.:** Brit. Med. J., **1**, 274, 1956.
59. **Tracey, M. L.,** and **Donovan, E. J.:** J. Am. Med. Assn., **146**, 1511, 1951.
60. **Vannini, P.,** and **Ippolito, A.:** Arch. patolog. e clin. med., **33**, 70, 1956.
61. Iidem: Ibid., **33**, 113, 1956.
62. **Volwiler, W., Bollman, J. L.,** and **Grindley, H.:** Proc. Mayo Clin., **25**, 31, 1950.
63. **Weech, A., Reeves, E.,** and **Goettsch, E.:** J. Biol. Chem., **113**, 167, 1936.
64. **Whitman, J. F., Rossmiller, H. R.,** and **Lewis, L. A.:** J. Lab. & Clin. Med., **35**, 167, 1950.
65. **Whittlesey, R. H., Ingram, P. R.,** and **Riker, W. L.:** Ann. Surg., **142**, 1013, 1955.
66. **Zemansky, A. P.:** Am. J. Med. Sci., **175**, 489, 1928.
67. Case Records of the Massachusetts General Hospital, New England J. Med., **258**, 749, 1958.

SUMMARIO IN INTERLINGUA

Ascites: Considerationes Etiologic Con Attention Special Prestate Al Valor De Varie Constatationes Laboratorial Ab Le Puncto De Vista Del Diagnose

Super le base de un revista de 142 casos exhibiente le signo de ascites, insimul con previe investigationes per altere autores, le sequente conclusiones es formulate con respecto al patientes con ascites:

1. Le retention de colorante Bromsulphaleina es quasi semper anormal in cirrhosis e congestive disfallimento cardiac associate con ascites. Malignitate effectua o non effectua un prolongate retention de colorante.

2. Hypoalbuminemia de infra 4 g pro cento es commun in omne conditiones associate con ascites. Illo es le plus marcate in morbo renal, cirrhosis, e morbos neoplastic.

Le nivellos de globulina total del sero tende a attinger plus alte valores in cirrhosis que in le altere conditiones.

Il ha essite reportate que in cirrhosis associate con ascites, le electrophorogramma del proteinas seral monstra frequentemente un augmento del fraction de globulina gamma, durante que in malignitate associate con ascites, il es communmente le globulina alpha que es elevate.

3. Le apparentia del liquido ascitic es macroscopicamente sanguinose in circa un quarto de omne effusiones neoplastic. Altere conditiones produce sanguine de visibilitate al oculo inarmate in certe casos, sed iste phenomeno es specialmente rar al tempore del prime punctionage.

4. Le contento de proteina e le gravitate specific del liquido ascitic es grossiermente proportional le un con le altere. Si determinationes del contento de proteina pare producer resultatos de un levemente plus alte grado de fidelitate, le ration es probabilemente a trovar in inaccuratias del valores pro le gravitate specific. In cirrhosis e morbo renal, le proteina total es quasi semper infra 3 g pro cento (e le gravitate specific es generalmente infra 1,016), sed in congestive disfallimento cardiac le valores es generalmente supra ille cifras. In morbo neoplastic, tanto le proteina como etiam le gravitate specific varia extensemente. Ambes es alte in tuberculose del peritoneo.

5. Le proteina in le liquido ascitic depende non solmente del morbo responsabile sed etiam del nivello de albumina seral. Assi il es necessari prender ambe ille factores in consideration quando on interpreta le datos trovate in le analyse del liquido. Il ha essite postulate que determinationes del proportion inter le valores pro proteina (o albumina) in le sero e in le liquido ascitic es possibilemente plus significative ab le puncto de vista diagnostic que le valor del proteinas in le liquido ascitic per se.

Il non existe multe studios relative al electrophorogramma del proteinas de liquido ascitic. Le resultatos del existente studios de ille genere es summarisate.

6. Numerationes cellular ha un certe valor in corroborar le presentia de sanguine in le liquido ascitic. Concentrationes de plus que 10.000 erythrocytos per ml es frequente. Altere datos es de valor sub certe conditiones. Tales es discutite brevemente.

7. Studios cytologic pro malignitate se monstra positive in circa tres quartos del specimens ab patientes con morbo maligne. Varie sitos primari produce varie procentages de resultatos positive. Reportos falsemente positive es rar.

8. Ascites chylose occurre como resultato del damnification o obstruction del drainage lymphatic del intestinos. In le presente studio, ascites chylose esseva incontrate le plus frequentmente in casos de morbo neoplastic.

9. Es discutite brevemente plure causas de ascites le quales es plus rar.

THE PANSYSTOLIC REGURGITANT MURMUR: A SIMPLE METHOD OF IDENTIFYING ITS ANATOMIC SOURCE

By Louis A. Soloff, M.D.
PROFESSOR OF CLINICAL MEDICINE; CHIEF, DIVISION OF CARDIOLOGY

Felix Cortes, M.D.*
FELLOW IN CARDIOLOGY, DIVISION OF CARDIOLOGY

William L. Winters, Jr., M.D.
INSTRUCTOR IN MEDICINE

AND

Jacob Zatuchni, M.D.
ASSOCIATE PROFESSOR OF MEDICINE

(From the Department of Medicine, Temple University School of Medicine and Hospital, Philadelphia, Pennsylvania)

Pansystolic regurgitant murmurs in the adult are due to mitral regurgitation, tricuspid regurgitation and ventricular septal defects. There are no auscultatory or phonocardiographic criteria that distinguish with confidence at all times any one from the other two. For this reason, associated findings are sought to differentiate the three.

Mitral regurgitation and ventricular septal defect may occur as isolated lesions but may have, in addition to a pansystolic murmur, a short mid-diastolic murmur due to excessive flows through the mitral valve. The apical location of the murmur, its softer quality, its radiation to the left axilla, the large left atrium and the normal pulmonary artery are frequent characteristics of mitral regurgitation which help to differentiate this lesion from ventricular septal defect. But such differentiation may fail when the lesions are trivial or in severe cases associated with pulmonary hypertension.

Mitral regurgitation is frequently associated with mitral stenosis and tricuspid regurgitation almost always is. The oft quoted localization of the murmur of tricuspid regurgitation to the lower left sternal border and its increase with inspiration occurs in only about one in 10 instances (Sepulveda and Lukas[3]). It was for this reason that Lukas found a diagnosis of tricuspid regurgitation was most confidently made when the syndrome of atrial fibrillation, chronically enlarged liver, large right atrium and a low QRS_{V1} with a delayed intrinsicoid deflection was present.

Soloff *et al.*[5] have previously reported on the changes in some cardiac murmurs induced by an intravenous infusion of nor-epinephrin sufficient to raise the systemic arterial pressure 20 mm. Hg or more.

Herein, we illustrate the characteristic changes in the pansystolic murmurs of mitral regurgitation, ventricular septal defect and tricuspid regurgitation induced by intravenous norepinephrin.

1) Mitral regurgitation: Figure 1 is from a known instance of rheu-

*Supported by the Heart Association of Southeastern Pennsylvania.

matic heart disease with mitral regurgitation. Physical examination revealed a grade 3 pansystolic precordial murmur loudest at the apical region and transmitted to the axilla. A third sound was audible just lateral to the apical impulse and was followed by an early short diastolic rumble.

The phonocardiogram shows a pansystolic murmur at both the mitral and tricuspid regions. A third sound and an inconstant early diastolic murmur are also seen in the tracing from the apical region.

After an infusion of nor-epinephrin sufficient to raise the diastolic pressure 20 mm. Hg, there is a marked increase in the amplitude of the apical pansystolic murmur as well as the ventricular filling murmur which is now constant. The first sound is increased slightly in amplitude.

2) Ventricular septal defect: Figure 2 is from a known case of ventricular septal defect. Physical examination revealed a harsh pansystolic murmur audible at both the tricuspid and mitral regions and a split second sound at the pulmonic region.

After nor-epinephrin, the first sound again increased in amplitude but this time more so without, however, any significant change in the pansystolic apical murmur. In contrast the pansystolic tricuspid area murmur increased greatly in amplitude and was also detected farther to the right. The pulmonary component of the second sound is also greatly increased in amplitude.

3) Tricuspid regurgitation: Figure 3 is from a known case of tricuspid regurgitation with tight mitral stenosis. Actually, this patient underwent open heart surgery for

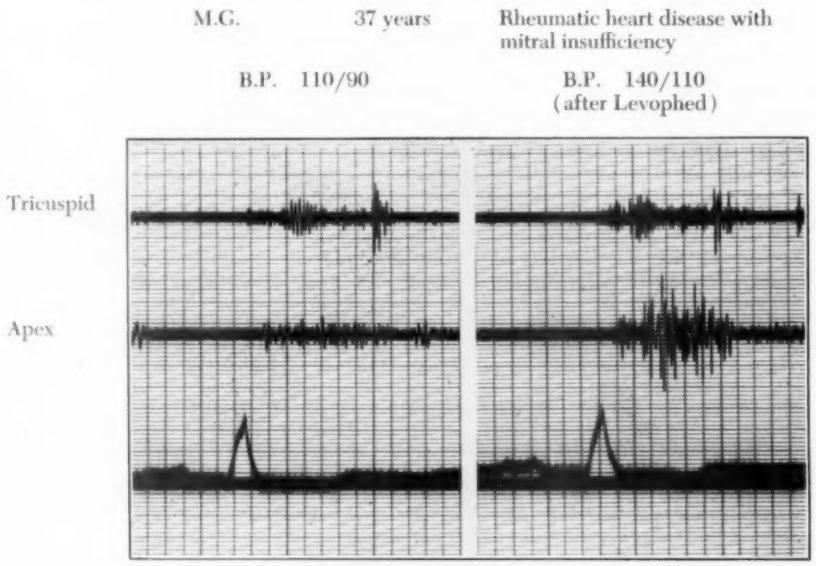


Fig. 1

B.M. 23 years — Intraventricular septal defect

B.P. 120/60 — B.P. 150/80 (after Levophed)

Tricuspid

Apex

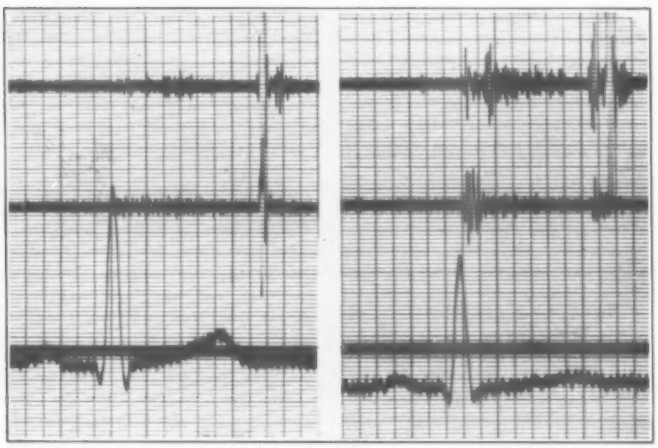


Fig. 2

C.P. 35 years — Rheumatic heart disease with mitral stenosis and tricuspid regurgitation

B.P. 120/80 — B.P. 170/100 (after Levophed)

Apex

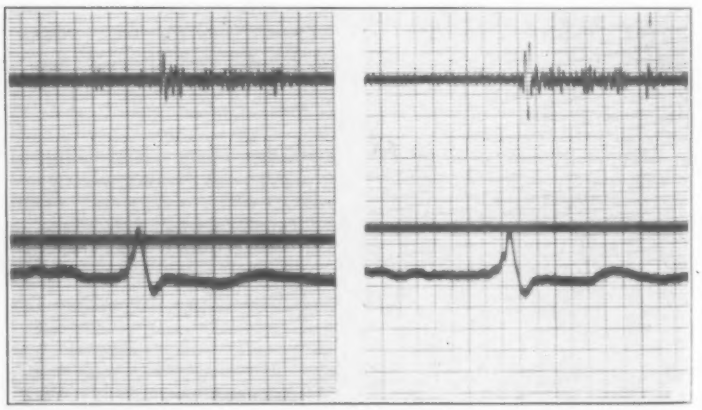


Fig. 3

mitral stenosis and regurgitation, a diagnosis suggested by all studies except phonocardiography after nor-epinephrin. She had had a mitral valvotomy 5 years previously for mitral stenosis. She did comparatively well for one year and then slowly and progressively deteriorated. Physical examination disclosed a pansystolic and a prolonged diastolic murmur.

After nor-epinephrin, there is again an increase in the amplitude of the first sound and also that of the diastolic murmur. But the pansystolic murmur remains unchanged.

Discussion. The characteristic changes in the pansystolic murmurs induced by nor-epinephrin are easy to understand.

The principal effect of raising the systemic diastolic arterial pressure is to increase the resistance to forward outflow from the left ventricle.

If mitral regurgitation is present, retrograde flow through the mitral valve will increase (Braunwald, Welch and Morrow[1]). Consequently, the apical pansystolic murmur will increase in amplitude.

If ventricular septal defect is present, retrograde flow through the defect will increase. Consequently, the pansystolic murmur at the tricuspid region will increase in amplitude and may be audible (and recorded) even farther to the right. The increased flow and pressure transmitted through the pulmonary valve will accentuate the pulmonic component of the second sound. If the increase in flow is considerable, the split between the aortic and pulmonic components of the second sound may widen.

On the other hand, increased resistance to forward outflow of the left ventricle does not affect or at least does not increase the flow through the tricuspid valve. Hence, nor-epinephrin does not appreciably change the murmur due to this lesion.

We should like to emphasize that we do not state that mitral regurgitation, tricuspid regurgitation and ventricular septal defects always produce pansystolic murmurs. This generalization maintained by Leatham[2] and most others who have made special studies of these lesions is an extrapolation of personal experience fortified by the fact that the pressure in the donor chamber is higher throughout systole than that of the recipient chamber. It is possible, however, that the two chambers are not in constant communication throughout systole. It is possible that ventricular contraction may sufficiently contract the mitral and tricuspid rings to make these otherwise incompetent valves competent sometime during systole. A similar mechanism could suffice for a small ventricular septal defect. These possibilities will be discussed in another communication. Meanwhile, we agree with Sprague[4] that the typical patterns of pan- and nonpansystolic murmurs are not always to be relied upon in differentiated diagnosis.

Summary. Nor-epinephrin is capable of differentiating the pansystolic murmur of mitral regurgitation, ventricular septal defect and tricuspid regurgitation: it produces no changes in the murmur of tricuspid regurgitation, increases the apical murmur of mitral regurgitation and increases the tricuspid murmur of ventricular septal defect as well as accentuating the pulmonary component of the second sound.

REFERENCES

1. Braunwald, E., Welch, G. H., and Morrow, Q. G.: J. Clin. Invest., **37**, 35, 1958.
2. Leatham, A.: Circulation, **17**, 601, 1958.

3. **Sepulveda, G.,** and **Lukas, D. S.:** Ibid., **11**, 552, 1955.
4. **Sprague, H. B.,** and **Ongley, P. A.:** Ibid., **9**, 127, 1954.
5. **Soloff, L. A., Wilson, M. F., Winters, W. L., Jr.,** and **Zatuchni, J.:** Ibid., **18**, 583, 1958.

SUMMARIO IN INTERLINGUA

Le Murmure Pansystolic De Regurgitation: Un Simple Methodo Pro Identificar Su Base Anatomic

Nor-epinephrina es capace de differentiar le murmure pansystolic de regurgitation mitral, de defecto ventriculo-septal, e de regurgitation tricuspidal. Illo effectua nulle alteration in le murmure de regurgitation tricuspidal; illo augmenta le murmure apical de regurgitation mitral; e illo augmenta le murmure tricuspidal e accentua le componente pulmonar del secunde sono in defecto ventriculo-septal.

SUMMARIO IN INTERLINGUA

(See page 759 for original article)

Un Electricamente Balanciate Systema Vectocardiographic Bipolar: Analyse E Synthese De Derivation, Utilisante Le Factor dR

Si on cognosce le influentia relative del distantia e del resistentia (*i.e.* factor dR) inter le puncto de origine e varie punctos al superficie del corpore, le ver characteristicas electric de omne derivation pote esser evalutate. Un methodo pro le analyse de derivationes describite. Per medio de un utilisation del factor dR, nove derivationes con predicibile characteristicas pote esser elaborate. Es presentate un methodo pro obtener derivationes a coordinatas X, Y, Z con ver balancia electric. Es describite un exemplo de un vectocardiogramma obtenite ab iste schema de referentias. Le circuito electric e le instrumento construite pro registrar le electricamente balanciate vectocardiogramma es illustrate.

SUMMARIO IN INTERLINGUA

(See page 771 for original article)

Inhibition Del Mobilisation De Lipidos De Stress Chirurgic Per Partialmente Dispolymerisate Acido Hyaluronic

Un partialmente dispolymerisate acido hyaluronic (PDAH) esseva administrate per via oral in doses de inter 400 e 3.000 mg a 9 patientes ante le effectuation de un operation intra-abdominal. Ben que augmentate quantitates de hormon de mobilisation de lipido (ML) esseva liberate a in le sanguine de omne iste patientes durante le curso del intervention chirurgic, mobilisation de lipido ab le depot omental non occurreva. Per consequente il pare que PDAH blocava le ML al omento.

Esseva notate nulle effectos adverse attribuibile a PDAH. Il es possibile que iste substantia va provar se de valor in statos hyperlipemic tanto acute como etiam chronic.

THE TREATMENT OF MUMPS ORCHITIS WITH PREDNISONE

By Edward S. Mongan, Capt. MC*

(From the Communicable Disease Service, William Beaumont Army Hospital, El Paso, Texas)

Although it is a self limited condition, epididymo-orchitis complicating mumps is quite distressing and disabling when it occurs. In the past, treatment has been symptomatic and far from dramatic in its results. Because the adrenal cortical steroids have an anti-inflammatory action, in recent years they have been tried for this condition. Some reported series have noted that the course of the disease is decreased both in severity and in length by using steroids (Petersdorf and Bennett[1], Zeluff and Fatherree[5]).

It is difficult to evaluate the results of a specific treatment in any benign, self-limited condition. Most of the reports of patients with mumps orchitis treated with steroids consist of small, uncontrolled groups in which the course of the disease in the treated patients is contrasted with the course as previously noted by the authors. Stenberg and Berry[4] used controls, but the physicians, and presumably the patients also, knew which patients were receiving the drug and which ones were not. Their conclusion that steroids were advantageous for moderately severe or severe mumps might have been swayed by their own enthusiasm for the drug. In an attempt to collect a large controlled series of patients with mumps orchitis treated with steroids at the same time in the same hospital, Smith and Bisher[3] reviewed the charts of 95 patients with mumps orchitis admitted to the Willard Parker Hospital in New York City. They obtained the largest series reported to date. It was, however, a retrospective study in which most of the pertinent information was taken from charts prepared by doctors and nurses unaware that a study would later be done. While physician bias is eliminated in such a study, the fact that the patients were cared for by many different doctors made uniform and consistent observations impossible. It is interesting, however, that the authors felt that cortisone was an analgesic in mumps orchitis, but they did not confirm the finding that the duration of fever or of hospitalization was decreased.

William Beaumont Army Hospital is a general hospital whose chief patient load is a number of young men from the nearby service installations. While no true epidemic of mumps has occurred in El Paso recently, sporadic cases are frequently seen. In an effort to further evaluate the use of steroids in mumps orchitis, a forward-looking, double blind study was conducted.

Material and Methods. Thirty consecutive patients with mumps orchitis were admitted to William Beaumont Army Hospital in a one-year period ending in June, 1958. As soon as the diagnosis was made clinically, each patient was placed on bed rest with bathroom privileges, scrotal support, ice bag to the scrotum, p.r.n., aspirin 0.6 gm. every 4 hours as needed for a temperature over 102° F., intravenous fluids if necessary, diet as tolerated, and Demerol 100 mg. every 4 hours as needed for severe pain. Oral temperatures were taken four times per day. Every patient in the study was observed by me throughout his entire hospitalization. When the testicular

*Present address: University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd., Rochester 20, New York.

swelling and tenderness had completely disappeared, the patient was ambulated on the ward for at least 48 hours prior to discharge. To insure uniform handling of the patients, they were all discharged to active duty within 72 hours after being ambulated with no limitations placed on their physical activities. Complete blood count, urinalysis, serological test for syphilis and chest roentgenograms were normal on all 30 patients.

The first 10 patients in this series received only the symptomatic therapy outlined above. The remaining 20 patients received 10 mg. q.i.d. of either prednisone or thiamine hydrochloride on a randomly selected basis. As soon as the diagnosis of mumps orchitis was made, an order was written for "pills for mumps orchitis." The nurse then consulted her previously determined master sheet, and gave the patient whichever drug came up next. To minimize any patient bias, the patients were not told that any study was being carried out, but were told that they were to receive pills that would benefit their orchitis. Throughout the study, I did not know which patients were receiving the steroids. The results were determined from the patient's charts and from the master sheet after all the patients involved had returned to active duty.

Results. The results are summarized in Table 1. There were no significant differences noted in the three groups in any characteristics analyzed. The age of the patients varied from 11 to 38 years. Except for the 11, 12 and 13-year-old dependent boys, all patients were on active duty with the Armed Forces. The three boys were handled the same as were the older patients for the purposes of this study. In all cases the diagnosis was a clinical one. No patient was included unless he had salivary gland involvement and obvious swelling and exquisite tenderness of a gonad. One patient who had only an orchitis was not included in the group in order to be certain that there would be no doubt about the diagnosis of mumps.

Six of the 30 patients were Negroes, which is roughly the proportion of Negro troops stationed in this area.

The orchitis appeared from 0 to 13 days after the parotitis, with all but 5 cases occurring from the third to the tenth day. In 17 patients, the orchitis was in the right testicle, in 11 in the left, and 2 patients had bilateral orchitis.

In the military service, patients with mumps parotitis are usually hospitalized. Since characteristically the orchitis develops after the parotitis, most of the patients in this series were treated as soon as their orchitis appeared. Only one-third of the patients were not started on treatment the day their orchitis began. One patient had the orchitis for 2 days before he was started on treatment and eight others were started after one day. All other patients were either already in the hospital when the orchitis started, or were hospitalized on the day it appeared. All patients with mumps parotitis were examined daily for orchitis and were told on admission to report to the doctor immediately if they noted any gonadal pain or swelling. The nine patients who were not hospitalized until after their orchitis was present for at least one day were all married men who had been allowed to stay at home when their illness first developed. Since the course of mumps orchitis is a short one, it is imperative that the patients be seen and treated as soon as possible in order to evaluate any therapy. A military hospital has the advantage over civilian hospitals in this regard, for in the latter, patients with parotitis are usually not hospitalized.

The duration of fever after the start of the mumps orchitis is an objective measurement which correlates roughly with the patient's course. As can be seen from Table 1, there was no significant difference in the duration of fever in any of the three groups.

As far as the patients are concerned the total time of hospitalization caused by the orchitis is a prime consideration.

TABLE 1.—DESCRIPTION AND TREATMENT OF THE 30 PATIENTS STUDIED

No. of Patient	*Age in Years*	*Race*	*Days after parotitis orchitis appeared*	*Gonad Involved*	*Duration of orchitis before Treatment (Days)*	*Days of fever after onset of orchitis*	*Days of hospitalization after onset of orchitis*	*Treatment*	*Total dose of prednisone in mg.*
1	26	Cau	6	Bilateral	0	5	14	None	
2	38	Cau	5	Right	0	3	7	None	
3	28	Neg	7	Right	0	7	10	None	
4	36	Cau	7	Right	0	5	11	None	
5	22	Cau	13	Right	1	1	11	None	
6	23	Cau	10	Right	0	3	9	None	
7	33	Cau	8	Left	0	3	11	None	
8	11	Cau	5	Right	1	3	8	None	
9	19	Cau	3	Left	0	0	9	None	
10	23	Cau	10	Left	0	2	12	None	
11	26	Neg	5	Right	0	3	12	Prednisone	230
12	30	Neg	3	Left	0	0	11	Prednisone	295
13	19	Cau	5	Bilateral	0	5	12	Thiamine	
14	17	Cau	8	Left	1	4	7	Prednisone	140
15	30	Cau	3	Right	1	5	12	Prednisone	225
16	32	Cau	1	Left	1	6	8	Thiamine	
17	35	Cau	8	Left	1	0	11	Thiamine	
18	21	Cau	3	Right	0	4	11	Thiamine	
19	29	Cau	6	Right	1	3	14	Prednisone	265
20	33	Cau	7	Right	0	5	10	Thiamine	
21	36	Cau	0	Right	2	2	8	Prednisone	150
22	12	Neg	7	Left	0	2	8	Prednisone	145
23	13	Cau	4	Right	1	3	9	Thiamine	
24	24	Cau	6	Right	0	4	11	Prednisone	215
25	28	Cau	3	Left	0	4	11	Thiamine	
26	22	Neg	5	Left	0	3	15	Thiamine	
27	28	Neg	12	Right	0	2	12	Prednisone	230
28	23	Cau	10	Left	0	4	9	Thiamine	
29	33	Cau	2	Right	0	7	13	Prednisone	240
30	20	Cau	3	Right	0	4	10	Thiamine	
Average for the symptomatically treated patients:						3.2 days	10.2 days		
Average for the patients who received thiamine:						3.8 days	10.6 days		
Average for the patients who received prednisone:						3.2 days	10.8 days		

By setting up criteria for discharge, I feel that I was able to gauge the time at which the patients were completely recovered on the different regimens. The total length of hospitalization was similar in the three groups.

The natural course of mumps orchitis, as demonstrated by the first 10 patients, is for the patient to be quite uncomfortable for 48 to 72 hours, for him to be febrile for 3 to 4 days, and for the swelling to disappear in 6 to 8 days. An attempt was made at the beginning of the study to estimate daily the amount of testicular swelling in each patient. This attempt was soon discontinued because I felt that it was too subjective. Moreover since the complete disappearance of gonadal swelling and tenderness was used as a criterion for ambulation, and subsequently for discharge from the hospital, I felt that the length of hospitalization was a more objective measurement of the effectiveness of a regimen.

Approximately one-half of the patients had at least one dose of Demerol for pain. Since the pain threshold varies markedly in different people, the total dose of narcotic given is not truly an objective measurement of the effectiveness of a regimen. There was, however, no difference noted between the patients on steroids and the other patients as far as the amount of narcotic given.

In the previously reported series, cortisone, ACTH, and hydrocortisone have been used. Because it seems to be just as effective and yet has fewer side-effects, prednisone is now being widely used in place of cortisone. I think, therefore, that the type of steroids used in this series should show comparable effects to the steroids used in other studies. The patients were started on prednisone as soon as a doctor verified the diagnosis of mumps orchitis and were continued on the drug until they left the hospital. The range of total prednisone given varied from 140 to 265 mg., with an average dose per patient of 205 mg.

Discussion. An analysis of the results obtained in this double blind study does not confirm the beneficial effects previously found in using adrenal cortical steroids in the treatment of mumps orchitis. Several factors may explain this difference. First, this is the first reported series in which both physician and patient bias was completely controlled. Second, the type of patient load seen in military hospitals makes the collection of such a series easier than it is in civilian hospitals. Moreover, the patients are usually hospitalized prior to the onset of their orchitis, so that therapy can be started as soon as the diagnosis is made. This is an obvious advantage in treating a short, benign illness where the patient will improve without any specific therapy. Third, this was a forward-looking series in which all the patients were seen daily by the same physician.

The study did confirm some previously noted observations. It seems generally agreed that if steroids are effective at all in mumps orchitis, only a short course of about 5 days is needed. This study showed no beneficial effect from a more prolonged use of the drug. In the dose given, moreover, no complications were noted. This finding is in agreement with most of the previously described series in which a short course of steroids was found to be relatively innocuous. Smith and Bisher[8] reported a 9.8% incidence of complications, but they were minor ones which could be easily treated with antibiotics. I feel that if the steroids did appreciably alter the course of mumps orchitis, the incidence of complications would be a hazard worth risking.

Several possibilities concerning the use of steroids in mumps orchitis were not explored in this study. Because of the difficulties in follow-up of military patients once they leave the hospital, no effort was made to see if the steroids had any effect on the incidence of subsequent testicular atrophy. Riseman[2] reported that steroids used prophylactically did not prevent the appearance of orchitis. Since this series included only patients with known mumps orchitis, no one with only salivary gland involvement was included. In addition, the possibility that larger doses of steroids or that one of the other steroids might be efficacious has not been ruled out by this study. Since the dose of prednisone given was well within the therapeutic range, and since it is as effective in treating other conditions as is cortisone, this possibility seems unlikely to me.

Summary. A double-blind, forward-looking study comparing the results of therapy in patients with mumps orchitis treated either symptomatically, or with a placebo, or with prednisone; revealed no differences in the course of the disease in the three groups.

REFERENCES

1. **Petersdorf, R. G.,** and **Bennett, I. L., Jr.:** A.M.A. Arch. Int. Med., **99**, 222, 1957.
2. **Riseman, G. C.:** J. Am. Med. Assn., **162**, 875, 1956.
3. **Smith, I. M.,** and **Bisher, J. W.:** New England J. Med., **258**, 120, 1958.
4. **Stenberg, E. S.,** and **Berry, W. C.:** U.S. Armed Forces Med. J., **7**, 1414, 1956.
5. **Zeluff, G. W.,** and **Fatherree, T. J.:** Ann. Int. Med., **46**, 852, 1957.

SUMMARIO IN INTERLINGUA

Prednisona In Le Tractamento De Orchitis Parotiditic

Un studio double-blind e prospective, comparante le resultatos therapeutic in patientes con orchitis parotiditic tractate (1) symptomaticamente, (2) per un placeba, o (3) per prednisona, revelava nulle differentias in le cursos del morbo in le tres gruppos.

CORRELATION OF SMOKING HABITS WITH HEMOLYTIC STREPTOCOCCI AND ANTISTREPTOLYSIN O RESPONSES*

By Milton S. Saslaw, M.D.
DIRECTOR OF MEDICAL RESEARCH, NATIONAL CHILDREN'S CARDIAC HOSPITAL

AND

Murray M. Streitfeld, Ph.D.
BACTERIOLOGIST, NATIONAL CHILDREN'S CARDIAC HOSPITAL
ASSISTANT PROFESSOR OF MICROBIOLOGY, UNIVERSITY OF MIAMI SCHOOL OF MEDICINE

(From the Departments of Medical Research, National Children's Cardiac Hospital and the Department of Microbiology, University of Miami School of Medicine, Miami, Florida)

Epidemiological studies (Saslaw and Streitfeld[2,3]) on β hemolytic streptococci conducted in Miami, Florida, provided us with an excellent opportunity to investigate any possible relationship of smoking habits of adults to the prevalence of streptococci in the human throat. Accordingly, data on smoking habits were collected at the same time that throats were swabbed for isolation of streptococci and venous blood samples were drawn for streptococcal antibody determinations.

Method. From October, 1955, through May, 1956, 1,815 adults had their throats swabbed once according to a technique previously described (Saslaw and Streitfeld[2,3]). These adults were presumably healthy and fell into two categories, 800 Miami residents and 1,015 Eastern Airlines† personnel presenting themselves for routine physical examinations at the medical office of the airlines (in Miami). The Miami resident group was comprised of parents of children attending the diagnostic Outpatient Clinic of the National Children's Cardiac Hospital, blood donors of the John Elliot Blood Bank, Miami, and Blood Bank of Mt. Sinai Hospital, Miami Beach. Airline personnel resided either in Miami or elsewhere in the United States.

Duplicate swabbings were taken from the throats of each of the 1,815 adults. The swabs were plated within 2 hours on blood agar base (Difco) and on neopeptone infusion agar (Difco), each enriched with 4% defibrinated sheep blood‡. The plates were incubated and observed for the presence of β hemolytic streptococci according to previously described methods[2,3]. Venous blood samples were drawn from 1,612 individuals at the same time as the throat swabbings were done. These bloods were allowed to clot, centrifuged, the supernatant serums decanted into small glass bottles, and the bottles placed in the deep freeze (−5° C.) until June, 1956. At that time, antistreptolysin O (ASO) determinations were performed according to the method of Rantz and Randall[1] using commercial (Difco) streptolysin O.

An information form was completed on each participant. Data collected included dates of collection of samples, name, address, phone number, city of residence, unusual ports of call (for airline personnel), age, sex, color, occupation, and information on smoking habits. Each person was asked whether he smoked at the present time and, if not, whether he had ever done so. If the participant was a current smoker, the type (cigar, cigarette or pipe) was entered as well as the quantity (cigarettes 1 to 5, 5 to 20, or more than 20 daily; cigars or pipefuls 1 to 2, 3 to 5, or 6 or more daily). He also was asked the time of the last act of smoking prior to throat culturing, whether or not he commonly inhaled, how many years he had been smoking, the name of the brand of cigarettes and

*Supported in part by grants from Florida State Board of Health and the U.S. Public Health Service (H1738).

†Dr. Howard K. Edwards, Chief Medical Officer, Eastern Airlines, made this portion of the study possible.

‡Purchased from Hyland Laboratories, Los Angeles, California.

whether or not he used a filter tip. If a person had been a smoker in the past, the type of smoking, amount, time since quitting, and practice of inhaling were tabulated. Each smoking form then was coded and recorded on a standard IBM form.

Results. Of the 1,815 adults sampled by throat culturing, records are available on 1,813. Smoking data was omitted accidentally in one case; our results are presented for the remaining

TABLE 1.—DISTRIBUTION OF 195 BETA HEMOLYTIC STREPTOCOCCAL CULTURES ISOLATED FROM 1,812 PARTICIPANTS IN A SMOKING STUDY. MIAMI, FLORIDA, OCTOBER, 1955 TO MAY, 1956

Examined				*Group of β Hemolytic Streptococci Recovered*							*Total*
No.	*%*	*Sex*	*Color*	*A*	*B*	*C*	*F*	*G*	*NG‡*	*Cb§*	*No. Carrying β Streptococci*
Nonsmokers											
461	25.4	M	W	4	3	4	0	3	5	0	19
		M	C	0	0	0	0	0	0	0	0
		M	T	4	3	4	0	3	5	0	19
		F	W	1	2	2	0	0	1	0	6
		F	C	0	1	2	0	1	0	0	4
		F	T	1	3	4	0	1	1	0	10
Total				5	6	8	0	4	6	0	29
% of Strep. Group				12.50	13.04	25.00	0.00	16.67	16.22	0.00	14.87
% of Individuals				1.08	1.30	1.74	0.00	0.87	1.30	0.00	6.29
Past Smokers											
204	11.3	M	W	3	4	0	2	2	3	0	14
		M	C	0	0	0	0	0	0	0	0
		M	T	3	4	0	2	2	3	0	14
		F	W	1	0	0	0	0	0	0	1
		F	C	0	1	0	0	0	0	0	1
		F	T	1	1	0	0	0	0	0	2
Total				4	5	0	2	2	3	0	16
% of Strep. Group				10.0	10.87	0.0	14.29	8.33	8.11	0.00	8.21
% of Individuals				1.96	2.45	0.0	0.98	0.98	1.47	0.00	7.84
Present Smokers											
1147	63.3	M	W	26*	23	18	7	11	23	1(B+F)	109
		M	C	2†	0	2	0	0	0	0	4
		M	T	28	23	20	7	11	23	1	113
		F	W	3	12	3	4	6	5	1(C+G)	34
		F	C	0	0	1	1	1	0	0	3
		F	T	3	12	4	5	7	5	1	37
Total				31	35	24	12	18	28	2	150
% of Strep. Group				77.50	76.09	75.00	85.71	75.00	75.68	100.00	76.92
% of Individuals				2.70	3.05	2.09	1.05	1.57	2.44	0.17	13.08
Total											
1812	100.0	M	W	33	30	22	9	16	31	1	142
		M	C	2	0	2	0	0	0	0	4
		M	T	35	30	24	9	16	31	1	146
		F	W	5	14	5	4	6	6	1	41
		F	C	0	2	3	1	2	0	0	8
		F	T	5	16	8	5	8	6	1	49
Total				40	46	32	14	24	37	2	195
% Strep. Group				100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
% of Individuals				2.21	2.54	1.77	0.77	1.32	2.04	0.11	10.76

*Incl. 2(Ao+B), †Incl. 1 Ao+C, ‡NG=Nongroupable, §Cb=Combinations of more than 1 group. W=White; C=Colored; T=Total.

1,812 people studied. Of these, 461 (25.4%) never smoked, 204 (11.3%) smoked at some time in the past, while 1,147 (63.3%) were smokers at the time of culturing and blood sampling.

Table 1 presents the distribution of the β hemolytic streptococci recovered from the throats of 195 of the 1,812 participants, listed according to Lancefield groups of streptococci, as well as color, sex, and smoking habits of the individuals carrying these organisms. Although the smokers constitute 63.3% of the entire population, 76.92% of the β streptococci recovered were from the throats of smokers.

Statistical analysis of the relationship of smokers, nonsmokers and past smokers to the frequency with which β hemolytic streptococci were recovered from throat swabs indicated that the differences observed could have been due to chance less than once in a thousand times ($X^2 = 17.7309$; $p<0.001$).

When Group A β hemolytic streptococci alone are considered, 77.50% were recovered from the throats of smokers ($X^2 = 7.0813$; $p<0.05>0.02$). All other groups of β hemolytic streptococci were isolated from the throats of smokers more frequently than from the non- and past smokers; differences were greatest in Group F, then, in decreasing order, nongroupable, Group B, G and C strains.

The percentage of individuals within each smoking category is indicated also in Table 1: 2.70% of present smokers yielded Group A streptococci, while 1.96% of past smokers and 1.08% of nonsmokers harbored these organisms.

Analysis of data collected on the 1,351 past and present smokers showed that cigarette smokers who consumed more than a pack per day were only slightly more prone to harbor streptococci than those individuals who smoked less. Similarly, β hemolytic streptococci were recovered from the throats of heavy cigar smokers relatively more frequently (33.3%), than might have been anticipated from the number of heavy cigar smokers in the noncarrier group (8.7%). Pipe smokers and cigar smokers, harboring β hemolytic streptococci in their throats, however, accounted for only 7.8% of the total group of individuals who smoked.

Antistreptolysin O titers are available for 1,611 of the 1,812 participants (Table 2). Averages were tabulated according to the smoking habits and group of β hemolytic streptococci recovered. Group A organisms were associated with the highest ASO titers (128 Todd units), Group G (104 units) and C (86 units), while the average of these determinations were lowest for those associated with Group B (71 units), F (81 units) or nongroupable strains (56 units) or where no organisms were isolated (71 units).

No unusual distribution of ASO titers was evident when the titers were considered from the standpoint of sex, age, race, smoking habits or streptococcal recovery.

Discussion. Smokers' throats yielded β hemolytic streptococci more frequently than nonsmokers or past smokers; 150 of 1,147 smokers (13.03%) were positive, while only 45 of 665 non- and past smokers (6.77%) had these organisms recovered from their throats. This difference is statistically very significant, its likelihood of being due to chance is less than once in 1,000 times. When Group A β hemolytic streptococci are considered alone, 31 strains were recovered from 1,147 smokers' throats (2.70%) and 9 from 665 non- and past smokers (1.35%); this difference is likely to be due to chance about three times in a hundred. The statistical significance of the effect of smoking on individual groups of β hemolytic streptococci can be evalu-

TABLE 2.—DISTRIBUTION OF ASO TITERS OBSERVED IN 1611 BLOOD SAMPLES, TABULATED ACCORDING TO FINDINGS OF β HEMOLYTIC STREPTOCOCCI IN SIMULTANEOUSLY COLLECTED THROAT CULTURES, AND ACCORDING TO SMOKING HABITS. STREPTOCOCCAL SMOKING STUDY. MIAMI, FLORIDA, OCTOBER, 1955 TO MAY, 1956.

	Groups of β Hemolytic Streptococci Recovered																*No. β hem. strep. recovered*		*Totals*	
	A		*B*		*C*		*F*		*G*		*Non-groupable*		*More than 1 group*		*Totals*					
Smoking Habits	*No.*	*Titer**	*No.*	*Titer*	*No.*	*Titer*	*No.*	*Titer*	*No.*	*Titer*	*No.*	*Titer*	*No.*	*Titer*	*No.*	*Titer*	*No.*	*Titer*	*No.*	*Titer*
Nonsmokers	4	110	6	84	7	126	0	—	3	180	6	78	0	—	26	109	395	76	421	78
Past Smokers	2	146	5	57	0	—	2	31	2	69	3	50	0	—	14	66	165	74	179	73
Present Smokers	30	120	32	71	22	74	12	90	11	89	25	52	1	166	133	85	878	69	1011	71
Total	36	125	43	71	29	86	14	81	16	104	34	56	1	166	173	87	1438	71	1611	73

*Average titer in Todd units.

ated more definitely only if larger samples are available.

Antistreptolysin O titers failed to reveal any clear cut differences between present smokers, past smokers and nonsmokers. Higher titers were associated with streptococcal recoveries, particularly in association with Group A and to a lesser extent with Groups G and C β hemolytic streptococci, regardless of the smoking habits of the individuals studied.

The association of present smoking with a higher frequency of recovery of β hemolytic streptococci may be due to the action of the products of smoking on the streptococci making the organisms more tenacious on host tissues, or making the tonsillar tissues more receptive to the organisms. Investigation of the effect of tobacco smoke on the growth of β hemolytic streptococci *in vitro* in artificial media and in tissue culture might help to indicate the mechanism of the relationship of smoking to the rate of recovery of β streptococci from the throat.

The finding that nonsmokers from whose throats β hemolytic streptococci were recovered had a higher average ASO titer (109 units, Table 2) than did present smokers (85 units) may be fortuitous, or it may indicate an altered immunological pattern influenced by smoking. Even when streptococci were not recovered, the nonsmokers had higher average ASO titers and indices (76 units) than did present smokers (69 units).

Summary. The possible relationship of adult smoking habits to the frequency of recovery of β hemolytic streptococci from throat cultures was investigated. Analysis of findings from 1,812 throat swabbings showed that β streptococci were isolated from the throats of present smokers almost twice as often as from non- or past smokers. This difference is very significant statistically ($p<0.001$). Group A organisms also were isolated more frequently from smokers' throats, but this difference is not as great ($p<.05>0.02$).

Antistreptolysin O studies (1,611 samples) showed no appreciable differences in titers of serums from smokers when compared with those from nonsmokers.

The higher frequency of streptococcal isolation among smokers than nonand past smokers may be due to an effect of smoke products on streptococci or on the mucous membrane barrier of the host.

REFERENCES

1. **Rantz, L. A.,** and **Randall, E.:** Proc. Soc. Exper. Biol. & Med., **59**, 22, 1945.
2. **Saslaw, M. S.,** and **Streitfeld, M. M.:** Pub. Health Report, **69**, 877, 1954.
3. **Streitfeld, M. M., Saslaw, M. S.,** and **Doff, S. D.:** Pub. Health Report, **71**, 745, 1956.

(Interlingua on page 709)

AN ELECTRICALLY BALANCED BIPOLAR VECTORCARDIOGRAPHIC SYSTEM: LEAD ANALYSIS AND LEAD SYNTHESIS USING THE dR FACTOR

By Lawrence E. Lamb, M.D.
PROFESSOR OF INTERNAL MEDICINE; CHIEF, DEPARTMENT OF INTERNAL MEDICINE

AND

George B. Smith, Jr., Major, USAF (MC)FS

(From the School of Aviation Medicine, Randolph Air Force Base, Texas)

The greatest obstacle to interpreting the relation of potential measurements from the body surface to the cardiac dipole has been the inability to evaluate the influence of distance and resistance between the dipole source and the surface point. When the position of the heart remains relatively fixed, the distance and consequently the resistance between the dipole center and a point on the body surface is the same, whether one is attempting to determine the influence of the X, Y or Z component of the dipole vector upon the point. In the preceding paper a method of determining the relative influence of distance and resistance (the dR factor) was set forth[6]. When such objective data are known the theoretical implications concerning whether resistance increases in proportion to the radius square as in the infinite volume conductor or whether the body is or is not a homogeneous volume conductor, a sphere, or a cylinder, matter very little indeed. It matters not at all whether the intervening tissue is bone, gas or blood. The only important point is the relative influence of distance and resistance between the dipole source and the surface point in question as related to other surface points. It is assumed that the practical application is the ultimate recording from such surface points and the proper analysis of measurements made at these points.

Once the dR factor for the various surface points over the body used for lead sites is known, one can analyze any given lead concerning its true coordinate axis or develop new coordinates with any axis at will. Moreover the sensitivity of any lead can be calculated, permitting equalization of the sensitivity (equilibration) for any combination of leads. Using the dR factor, this paper will demonstrate: lead analysis of a number of leads commonly used in vectorcardiography and the synthesis and equilibration of three electrically balanced mutually perpendicular leads for vectorcardiography. The circuit diagram and instrument for recording vectorcardiograms with their components utilized in this laboratory will be demonstrated.

LEAD ANALYSIS. The simplest lead to analyze is the true electrically balanced bipolar lead. A Y coordinate lead over the right back which has electrodes attached at two symmetrical points with equal dR factors is a good example (Fig. 1). The coordinate length of X (LX) is the same for each point, thus each point has the same potential relationship to the X component of the dipole vector (LX/dR is the same for both points). Since both electrode

sites are on the back the Z coordinate length (LZ) is the same for both points and each point has the same relationship to the Z component of the dipole vector (LZ/dR is the same for both points). The electrodes being of opposite sign (+, −) the X and Z components are cancelled out, leaving only the Y component. The lead truly represents the influence of only the Y component of the dipole vector. If the X component influence had not been equal at both points their potential difference would not have been zero and the X component would have influenced the potential difference measured between the two points. In that event the lead would not represent a true Y coordinate. A similar circumstance applies to the Z component. The Y coordinate lead over the back is one of the more accurate electrically balanced leads commonly used in vectorcardiography.

Several of the leads used to measure an X coordinate value of the dipole vector are not true X coordinates. Both the method of Grishman[3] and the method of Duchosal and Sulzer[1] use a bipolar lead over the lower posterior thorax. The negative and positive electrodes are equidistant from the spine. Although considerable variation exists between different subjects, the problem can be illustrated using the dR factor of two symmetrical points over the lower back (16 cm. below E point and 12 cm. to the right and left of the spine) (Fig. 2). The dR factor over the left posterior thorax at that point is only 0.65, whereas at the point over the right posterior thorax it is 1.00. Since the Y coordinate length from both points is the same (16 cm.), the point over the left back is much more sensitive to the Y component vector. Such a bipolar lead is significantly influenced by the Y component of the

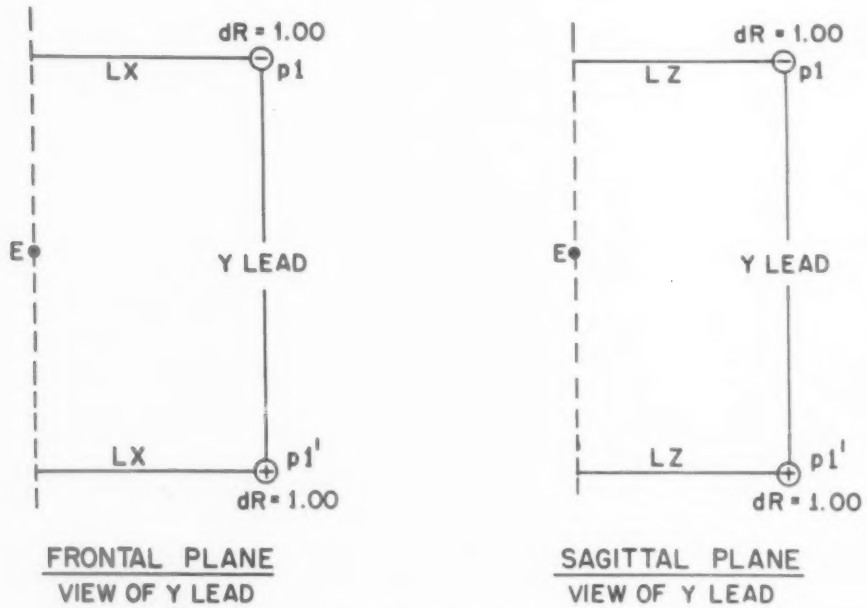


Fig. 1.—An electrically balanced Y lead (see text).

dipole vector. For similar reasons the lead is distorted by the Z component of the dipole vector. This lead is not a coordinate measuring the X component alone. The details for the calculation of the sensitivity for such a lead to X, Y and Z components is illustrated below.

For identification the point on the left back is designated pl and on the right back pr.

The voltage at a surface point in relation to a component vector is relative to coordinate length/dR. The relative contribution of the X, Y and Z components to pl are calculated as follows:

X component =
LX/dR = 8 cm./.65 = 12.3
Y component =
LY/dR = 16 cm./.65 = 24.6
Z component assuming LZ equals 16 cm. =
LZ/dR = 16 cm./.65 = 24.6

In the above illustration it is noted that pl is more sensitive to the Y and Z dipole components than it is to the X component.

The relative contributions of X, Y and Z components to pr are calculated as follows:

X component =
LX/dR = 16 cm./1.00 = 16.0

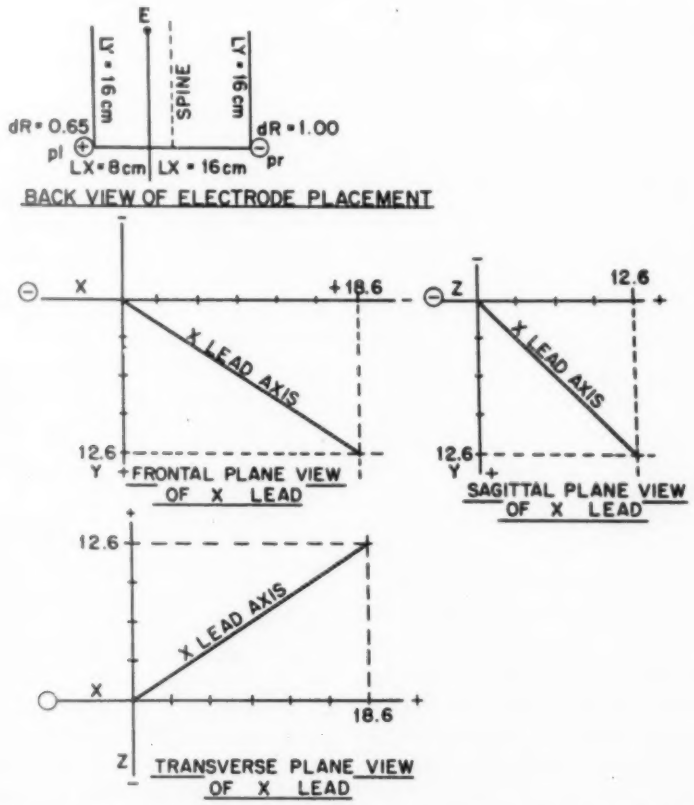


Fig. 2.—An unbalanced X lead over the back is illustrated at the top of the figure. The electrical axis of the lead as seen in the frontal, sagittal and transverse plane is demonstrated below (see text).

Y component =
LY/dR = 16 cm./1.00 = 16.0
Z component =
LZ/dR = 16 cm./1.00 = 16.0

Since potential difference is measured between pl and pr the equation
pl — pr equals potential difference, applies.
The relative X component contribution for the lead is calculated by substitution:

12.3 — (—16.0) = 12.3 + 16.0 = 18.3 units

The relative Y component contribution for the lead is

24.6 — (+16.0) = 12.6 units.

The relative Z component contribution is

24.6 — (+16.0) = 12.6 units.

In the above calculation the relative contributions of the X, Y and Z components of the dipole vector to such a bipolar lead was determined to be 18.3 units, 12.6 units and 12.6 units respectively. Whenever the relative sensitivity of a lead to all three component vectors is known, the true coordinate axis of the lead can be graphed in the frontal, sagittal and horizontal plane. The relative contributions in units for each component are merely plotted along their coordinate on the graph and a straight line drawn. Such a graph for the above lead is illustrated in Fig. 2.

A simple geometric lead over the back across the shoulders is similarly distorted. In this circumstance a positive electrode on the left above the Y component vector causes the X coordinate to be distorted upward as in the Burger triangle rather than downward.

The above example is not comparable to all the subjects studied by such bipolar leads across the back, as coordinate length is varied in different subjects and the dR factor for other locations is not quite the same; however, it does illustrate the direction of the distortion, if not the exact degree.

Leads commonly used to measure the Z component show distortions in a comparable manner to the X lead. The dR factor at a point over the anterior right thorax is roughly .80 of a comparable point over the right posterior thorax. The coordinate is distorted by both the X and Y components contribution to voltage at the two points.

LEAD SYNTHESIS. From the preceding lead analysis it is apparent that construction of a true X coordinate lead requires elimination of contributions from the Y and Z components. This is done by selecting points that have the same relative value for LY/dR which cancel out by the difference in polarity of the lead and elimination of the Z component in a like manner. It is desirable to choose surface points sufficiently remote from the heart to maintain the cardiac dipole effect. Numerous different combinations can be constructed. The combination of electrode sites discussed here are the ones utilized to synthesize three mutually perpendicular leads to act as X, Y and Z coordinates (Fig. 3).

The X coordinate lead has negative electrodes at p2 (16 cm. to the right and 12 cm. above the projection of E point on the back) and p2′ (symmetrically located below E point). The positive electrodes are attached at p17 (16 cm. directly above E point on the back) and p17′ (symmetrically located 16 cm. below E point). The dR factor at the positive electrode sites is 0.80 and at the negative electrode it is 0.87.

The Y component of the cardiac dipole is cancelled out between p2 and p2′ as negative electrodes are attached at both points and similarly it is cancelled out at p17 and p17′ since both

of these sites are attached to positive electrodes*

All four electrodes are on the back of the subject, thus the Z coordinate length (LZ) is nearly the same for all four locations. The dR factors are similar and the Z component received at the two negative electrodes approximates its influence at the two positive electrodes, enabling its cancellation. The end result is a combination of four electrodes that measure almost exclusively the X component and act as a true X coordinate lead. The comparative sensitivity of the lead equals the sum of LX/dR for each electrode†, or 36.7 units. This value is used later to equilibrate the three leads, X, Y and Z.

The Y coordinate lead is formed by placing a positive electrode at pl′ (16 cm. to the right and 16 cm. below the projection of E point) on the back and a negative electrode at pl (16 cm. symmetrically above the Y_0 plane). The dR factor for these two points is 1.00. LX is the same for both points as is LZ. This is a good Y coordinate lead, relatively uninfluenced by X or Z components. The relative sensitivity of the Y lead is

LY/dr — (—LY/dR) or

16 cm./1.00 + 16 cm./1.00 = 32 units.

The Z coordinate lead utilizes four electrodes, primarily to eliminate the

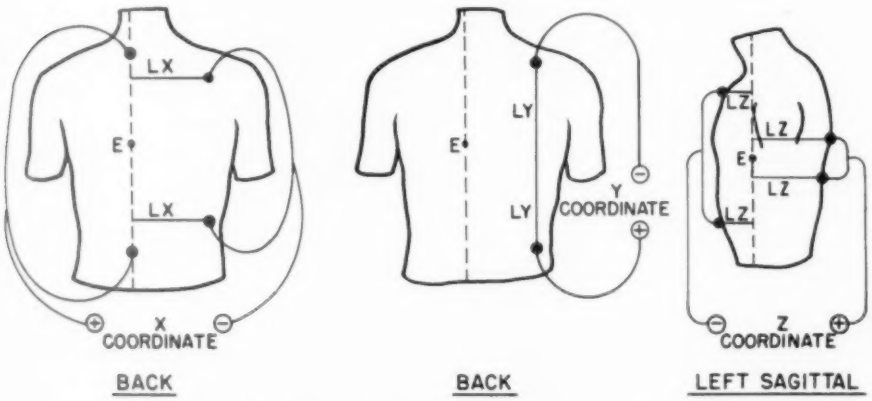


Fig. 3.—Electrode placement to synthesize X, Y and Z coordinate leads.

*The Y component at p2 (Vp_{2Y}) = LY/dR or 12 cm./0.87. This point is above the Y_0 plane and has a negative value (−12 cm./0.87. $V_{p2'Y}$ = LY/dR or 12 cm./0.87. Since this is below the Y_0 plane it has a positive value (+16 cm./0.87). Both electrodes are positive so their sum is,

$V_{p2'Y}$ + Vp_{2Y} or 12 cm./0.87 + (−12 cm./0.87) = 0

$Vp_{2'Y}$ + Vp_{2Y} or 12 cm./0.87 + (−12 cm./0.87) = 0

The Y component at p17 (Vp_{17Y}) = LY/dR or a negative 16 cm./.80.

$V_{p17'Y}$ is a positive 16 cm./.80.

The equation becomes

− (+16 cm./.80) − (−16 cm./.80) = 0

†Vp_{2X} = 16 cm./.87

$V_{p2'X}$ = 16 cm./.87

Vp_{17X} = 0/.80

$V_{p17'X}$ = 0/.80

(Vp_{17X} + $Vp_{17'X}$) − (−Vp_{2X} − $Vp_{2'X}$) =

0 + 16/.87 + 16/.87 = 36.7 units

influence of the Y component. Two positive electrodes are placed on the back at p4 and p4′ (16 cm. to the right and 4 cm. above or below the projection of E point on the back). Two negative electrodes are placed on the anterior surface at p26 and p26′ (16 cm. to the right and 12 cm. above or below the projection of E point on the anterior chest). The paired positive electrodes above and below the Y_0 plane over the back result in cancellation of the Y component between these two points. Similarly the two negative electrodes on the anterior surface result in cancellation of the Y component between these two points. The X coordinate length (16 cm.) is the same for all four surface points. The surface points chosen have nearly equal dR factors, thus the X component is cancelled out by the difference in electrode polarity except for minor influences due to individual differences in the dR factors.

With the subject lying on the back the dR factor for the four points used in the Z lead averages 0.70 for the subjects studied. The comparative sensitivity equals the sum of the four LZ coordinates divided by 0.70. The sum of the LZ coordinates equals the sum of the anterior posterior distance between p4 and p26 and between p4′ and p26′. These distances are measured on each subject. A common sum is 38 cm. (19 cm. + 19 cm.). It is apparent that locating the exact position of E point in its anterior posterior location is not essential to the calculation. The relative sensitivity of the Z coordinate must be calculated individually by first determining the sum of the LZ coordinate lengths from measurements taken directly from the body $\frac{(\text{LZ [sum]})}{(\quad .70 \quad)}$. A difference does exist between the flat-chested individual and the deep-chested individual. In the example used above the relative sensitivity of the Z coordinate lead is 54.3 units (38 cm./.70).

It is very important that all electrodes be properly placed. An electrode for the anterior thorax that is placed too high (above the level of the jugular notch) is not satisfactory for Z coordinate measurements. The Z coordinate at best will be minimally influenced by the X component due to differences in the dR factor between the anterior and posterior sites. Some subjects will be too small for the adult reference frame given above. Since the dR factors were established in the adult at 4 cm. intervals a simple conversion to intervals of 3 cm. or even 2 cm. can be used. When precision is a premium, individual dR factors can be obtained prior to synthesizing the three leads. By using cancellation techniques the true dR factor for the points used for lead attachment can be simply evaluated and the validity of dipole representation can be ascertained at the same time.

It is of interest that the three leads described above appear to have nearly true X, Y, Z coordinate characteristics (mutually perpendicular) when mapped on the image surface diagrams of Frank[2]. However, Frank's work involves a limited number of experiments. Minor differences in relative lead sensitivity is noted. The X coordinate calculated from the dR factor is slightly more sensitive than the Y coordinate, whereas by Frank's image surface diagram the Y coordinate is slightly more sensitive than the X coordinate. Nevertheless, it is interesting that the phantom model studies have come so close to the actualities of the problem.

LEAD EQUILIBRATION. Although the X, Y, Z leads present the characteristics of mutually perpendicular coordinates

they have different relative sensitivity factors. Their sensitivity can be equalized (equilibrated) by adjusting the amplification for each lead on the recording instrument. The desired amplification is chosen for one lead (for example, 1 mv. = 2 inches for the X lead) and the other leads are equilibrated to it.*

When X lead amplification in 1 mv. = 2 inches the Y amplification is calculated from the formula

$$\text{Y amplification} = \text{X amplification} \times \frac{\text{X coordinate sensitivity}}{\text{Y coordinate sensitivity}}$$

or by substitution

$$= 2.0 \times \frac{36.7 \text{ units}}{32.0 \text{ units}}$$

$$= 2.3 \text{ inches for 1 mv.}$$

The Z amplification is calculated from the formula

$$\text{Z amplification} = \text{X amplification} \times \frac{\text{X coordinate sensitivity}}{\text{Z coordinate sensitivity}}$$

or

$$= \text{X amplification} \times \frac{\text{X coordinate sensitivity}}{\text{sum of LZ/dR}}$$

and in this example

$$= 2.0 \times 36.7 \times \frac{.70}{38}$$

$$= 1.61 \text{ inches for 1 mv.}$$

When the amplification is adjusted so that 1 mv. creates the above calculated deflections the recording instrument records true X, Y and Z leads that are equal in sensitivity. It should be pointed out that none of the electrodes are over the left chest or near the heart. The locations used are acceptable for representation of the electrical cardiac cycle as a changing dipole.

The X, Y and Z leads are introduced into a simple circuit through Grass pre-

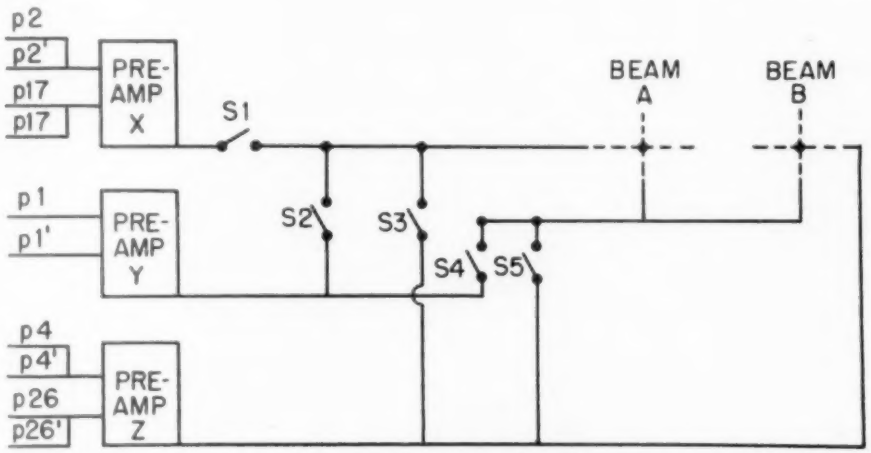


Fig. 4.—Circuit for recording the electrically balanced VCG reference system.

amplifiers to be presented on a Dumont oscilloscope. The circuit (Fig. 4) and arrangement of the instrument (Fig. 5) was designed by one of us (LEL). A normal vectorcardiogram recorded by this means is depicted in Fig. 6.

Utilizing a precision instrument with the subject in a shielded cage, very large amplifications are easily obtained to study the P or T loop and the details of the center. The X, Y and Z leads are also graphed on a time base on a moving film strip.

APPLICATION. The use of a balanced vectorcardiographic reference system enables recording relatively undis-

*The oscilloscope screen utilizes the inch scale and this laboratory ordinarily uses a standardization so that 1 mv. produces 2 inches of deflection on the scope for the X lead.

torted measurements of the changing cardiac dipole. Preliminary use indicates that it is useful in the exclusion of the diagnosis of inferior wall myocardial infarction. Many examples of Q3, QaVf problems are due to the characteristics of the body as a conductor. Using the electrically balanced leads, many of these cases are shown to have normally oriented initial spatial forces, whereas in the presence of infarction the initial forces are directed away from a myocardial area. This point will be discussed in detail in another publication.

Many of the projected uses of the vectorcardiogram can now be adequately investigated. The significance of the length of the vectorcardiographic loop itself has been recognized (polygon theorem) and related to a function of absolute potential of the heart in

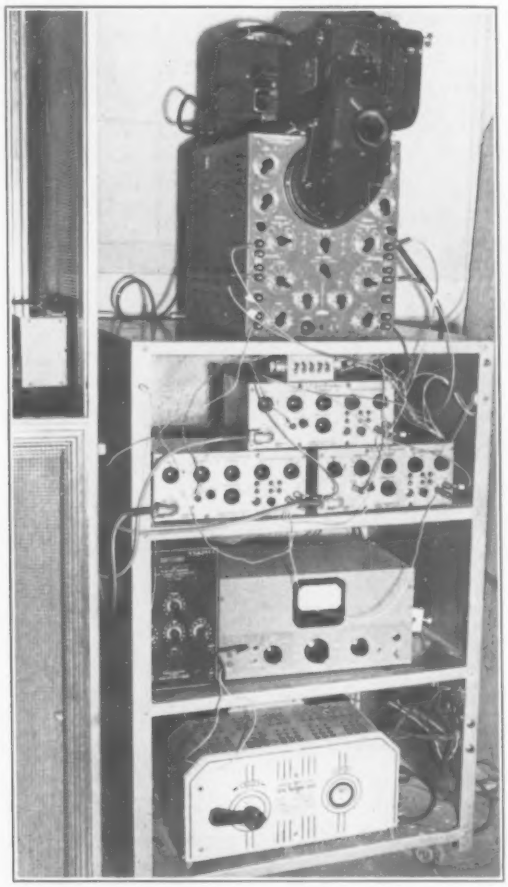


Fig. 5.—The recording instruments for the vectorcardiogram wired to a panel which permits rapid selection of leads. The panel contains additional circuits not diagrammed which permits versatility in lead selection for other reference systems as well as its use for other research. The patient is enclosed in a screened cage which is grounded.

contradistinction to resultant voltage expressed by instantaneous vectors (Lamb[4]). A method has been developed to depict simultaneously the X, Y and Z coordinate measurements, the successive resultant instantaneous vectors, and the VCG arc swept out by the changing vector, for the entire electrical cardiac cycle, along a linear time base (Lamb[5]). This is called the linear vectorcardiogram. By using the electrically balanced reference system, measuring the length of the VCG arc and utilizing the linear vectorcardiogram many new facets of the electrical activity of the heart can be explored.

Summary. If one knows the relative influence of distance and resistance (dR factor) between the source and various points over the body surface, the true electrical characteristics of any lead can be evaluated. A method of lead analysis is described. Utilizing the dR factor new leads which have predictable characteristics can be devised. A method for obtaining true electrically balanced X, Y, Z coordinate leads is developed. An example of a vectorcardiogram obtained from this reference frame is depicted. The electrical circuit and instrument designed to record the electrically balanced VCG are illustrated.

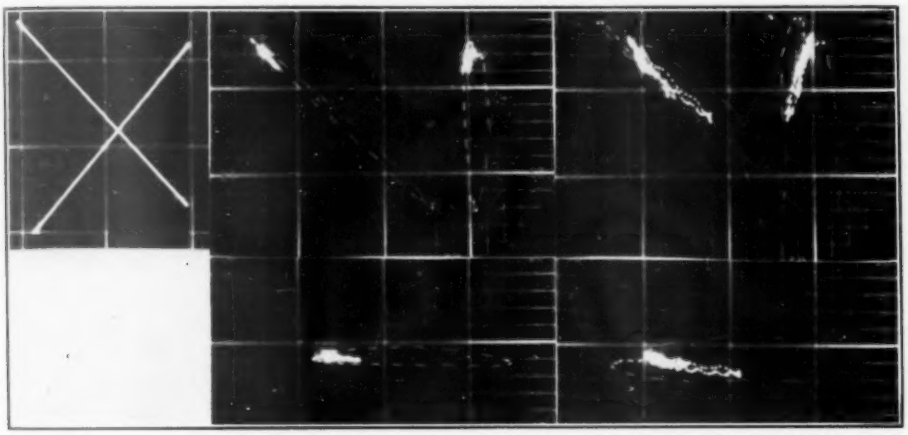


Fig. 6.—This is a normal VCG recorded with the balanced reference system. The cross bars (left) indicate the amplification for the X, Y and Z inputs. The frontal and sagittal views of the vectorcardiogram are depicted in the upper center. The transverse view is depicted in the bottom center photograph. A blow-up, to see the loop center details, is on the right.

REFERENCES

1. **Duchosal, P. W., and Sulzer, R.:** La Vectorcardiographie. Basel: S. Karger, 1949.
2. **Frank, E.:** Am. Heart J., **47**, 757, 1954.
3. **Grishman, A., Brown, E. R., and Jaffe, H. L.:** Am. Heart J., **41**, 483, 1951.
4. **Lamb, L. E.:** Fundamentals of Electrocardiography and Vectorcardiography. Springfield, Ill.: Charles C Thomas, 1957.
5. Idem: Am. J. Cardiology, in press.
6. **Lamb, L. E., and Smith, G. B.:** Am. J. Med. Sci., **237**, 612, 1959.

(Interlingua on page 748)

LACTIC DEHYDROGENASE VERSUS GLUTAMIC OXALACETIC ACID TRANSAMINASE AS A DIAGNOSTIC TEST FOR MYOCARDIAL INFARCTION

By Irving Freeman, M.D.

CHIEF, MEDICAL SERVICE, VETERANS ADMINISTRATION HOSPITAL, FORT HOWARD, MARYLAND; ASSISTANT PROFESSOR OF MEDICINE, UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE, BALTIMORE, MARYLAND

Deborah A. Jackson, B.S.

BIOCHEMIST, GENERAL MEDICAL RESEARCH LABORATORY VETERANS ADMINISTRATION HOSPITAL, FORT HOWARD, MARYLAND

AND

Charles S. Collier

MEDICAL BIOLOGY TECHNICIAN, GENERAL MEDICAL RESEARCH LABORATORY, VETERANS ADMINISTRATION HOSPITAL, FORT HOWARD, MARYLAND

(From the Department of Medicine and General Medical Research Laboratory, Veterans Administration Hospital, Fort Howard, Maryland)

LaDue, Wroblewski and Karmen[5] in 1954 first demonstrated the value of estimating the levels of serum enzymes of patients suffering acute myocardial infarction. Since then, determinations of lactic dehydrogenase and glutamic oxalacetic acid transaminase have proven to be very useful tools in the diagnosis of this condition. Numerous investigators (Hanson and Biörck[2], Hsieh and Blumenthal[3], MacDonald *et al.*[6], Miller[7], Richardson *et al.*[9], Wacker *et al.*[11], White[12], Wroblewski and LaDue[14], Zimmerman and Weinstein[15]) have reported on the relative merits of one enzyme level estimation over the other. Some felt that the determination of lactic dehydrogenase was easier to perform and that increased values were noted over a longer period of time than was the case with transaminase. Others were of the opinion that the higher initial levels of transaminase served to make this determination more specific. It would appear worthwhile therefore to assemble data comparing the serum concentrations of these enzymes as initially determined in patients admitted between 12 and 48 hours after the onset of symptoms, the period of time when most patients are admitted for this condition. Conclusions then may be drawn as to which test should be executed at a time when the results would be of greatest value.

Materials and Methods. Sixty consecutive patients admitted between 12 and 48 hours after the onset of symptoms referable to a myocardial infarction were studied. All had classical symptoms and either typical serial electrocardiographic changes or postmortem evidence of acute myocardial infarction. On admission blood was drawn for concomitant determination of the level of serum glutamic oxalacetic acid transaminase and lactic dehydrogenase.

The former was determined by a method which, in principle, is outlined by Steinberg *et al.*[10]: 0.1 ml. of test serum, 0.5 ml. of aspartic acid, 0.1 ml. of malic dehydrogenase, 0.1 ml. of reduced diphosphopyridine nucleotide and 2.0 ml. of phosphate buffer (pH 7.4) were thoroughly mixed in a test tube, and 0.1 ml. of test serum, 0.5 ml. of aspartic acid, 0.1 ml. of malic dehydrogenase and 2.1 ml. of phosphate buffer (pH 7.4)

were mixed in a control tube. Both were permitted to stand for 30 minutes at room temperature. Then 0.2 ml. ketoglutaric acid was added to each tube. Two minutes later the optical density at 340 mμ was read in a Beckman DU spectrophotometer. At 2-minute intervals thereafter, for a period of 18 minutes, readings were made and then the activity per minute per ml. was calculated. Using as a unit (Karmen[4]) "the amount of enzyme that will cause the reading to decrease at the rate of 0.001 O.D. units per minute per cm. light path at 25° C.," the activity was converted into units. Fifty units (Chinsky *et al.*[1], Ostrow *et al.*[8]) were considered to be the upper limits of normal.

Lactic dehydrogenase was determined by the method which, in principle, is outlined by Wroblewski and LaDue[14]: 0.1 ml. of test serum, 0.1 ml. of reduced diphosphopyridine nucleotide and 2.4 ml. of phosphate buffer (pH 7.4) were thoroughly mixed in a test tube. And 0.1 ml. of test serum and 2.5 ml. of phosphate buffer (pH 7.4) were mixed in a control tube. Both were permitted to stand 20 minutes. Then 0.1 ml. sodium pyruvate was added to each tube. Two minutes later the optical density at 340 mμ was read in a Beckman DU spectrophotometer. At 2-minute intervals thereafter, for a period of 18 minutes, readings were made and then the activity per minute per ml. was calculated. The activity was converted into units, the unit being the same as that defined under the transaminase determination; 600 units were considered to be the upper limits of normal (470 ± 130) (Wroblewski and LaDue[14]).

Results. The following table exhibits comparative values of the enzyme levels at the times of admission of patients to the hospital.

TABLE 1.—COMPARATIVE VALUES OF ENZYME LEVELS AT TIME OF ADMISSION TO HOSPITAL

	S.G.O.T.	*L.D.H.*		*S.G.O.T.*	*L.D.H.*
1.	63	210	31.	61	**800**
2.	180	420	32.	79	**610**
3.	223	443	33.	72	510
4.	52	**620**	34.	61	390
5.	102	**910**	35.	200	440
6.	240	**780**	36.	110	510
7.	186	**880**	37.	98	**900**
8.	350	**2000**	38.	73	**800**
9.	190	**1250**	39.	82	**1110**
10.	165	**1250**	40.	150	**1000**
11.	62	**1025**	41.	160	**1110**
12.	2450	**3500**	42.	53	370
13	292	**1160**	43.	77	**880**
14.	150	570	44.	255	**1140**
15.	70	340	45.	55	550
16.	67	**910**	46.	56	330
17.	85	310	47.	53	**4250**
18.	75	**1090**	48.	184	**1450**
19.	74	**820**	49.	67	290
20	123	**930**	50.	63	400
21	61	280	51.	140	**770**
22.	55	**880**	52.	68	**690**
23.	120	330	53.	55	220
24.	60	500	54.	115	**1170**
25.	55	**770**	55.	144	520
26.	290	400	56.	103	500
27.	246	**825**	57.	280	**670**
28.	86	280	58.	110	**1400**
29.	54	**660**	59.	52	260
30.	280	**1600**	60.	63	400

Bold numbers identify elevated values of L.D.H.

DISCUSSION. All of the levels of the serum glutamic oxalacetic acid transaminase were elevated. In general, the values of the serum lactic dehydrogenase were also elevated, but 25 were within the normal range. With the techniques and standards used in this study, then, it would appear that if one were to rely upon a single test to be performed between 12 and 48 hours after the onset of the initial symptoms, the determination of transaminase would be the test of choice in corroborating a diagnosis of myocardial infarction.

Summary. Simultaneous determinations of the levels of serum glutamic oxalacetic acid transaminase and serum lactic dehydrogenase were made on 60 patients between 12 and 48 hours after the onset of the initial symptoms of acute myocardial infarction. Classical histories plus serial electrocardiographic changes or necropsy evidence of infarction verified the presence of such lesions. All of the patients exhibited elevated levels of transaminase, whereas only 35 of the 60 patients had elevated levels of lactic dehydrogenase. If a single test were to be employed to confirm an impression of acute myocardial infarction between 12 and 48 hours of its occurrence, the assay of transaminase would appear to be significantly superior to that of lactic dehydrogenase.

REFERENCES

1. **Chinsky, M., Shmagranoff, M. D.,** and **Sherry, S.:** J. Lab. & Clin. Med., **47**, 108, 1956.
2. **Hanson, A.,** and **Biörck, G.:** Acta med. Scandinav., **157**, 493, 1957.
3. **Hsieh, K. M.,** and **Blumenthal, H. T.:** Proc. Soc. Exper. Biol. & Med., **91**, 626, 1956.
4. **Karmen, A.:** J. Clin. Investigation, **34**, 131, 1955.
5. **LaDue, J. S., Wroblewski, F.,** and **Karmen, A.:** Science, **120**, 497, 1954.
6. **MacDonald, R. P., Simpson, J. R.,** and **Nossal, E.:** J. Am. Med. Assn., **165**, 35, 1957.
7. **Miller, E. C., Jr.:** South. Med. J., **51**, 499, 1958.
8. **Ostrow, B. H., Steinberg, D., Ticktin, H. E., Polis, G. N.,** and **Evans, J. M.:** Circulation, **14**, 790, 1956.
9. **Richardson, D. E., Coker, S. D., Jr.,** and **Ray, C. T.:** Bull. Tulane Med. Fac., **17**, 45, 1957.
10. **Steinberg, D., Baldwin, D.,** and **Ostrow, B. H.:** J. Lab. & Clin. Med., **48**, 144, 1956.
11. **Wacker, W. E., Ulmer, D. D.,** and **Valee, B. L.:** New England J. Med., **255**, 449, 1956.
12. **White, L. P.:** Ibid., **255**, 984, 1956.
13. **Wroblewski, F.:** Am. Heart J., **54**, 219, 1957.
14. **Wroblewski, F.,** and **LaDue, J. S.:** Proc. Soc. Exper. Biol. & Med., **90**, 210, 1955.
15. **Zimmerman, H. J.,** and **Weinstein, H. G.:** J. Lab. & Clin. Med., **48**, 607, 1956.

SUMMARIO IN INTERLINGUA

Dishydrogenase Lactic Verso Transaminase De Acido Glutamic Oxalacetic, In Lor Valor Como Base De Un Test Diagnostic Pro Infarcimento Myocardial

Determinationes simultanee del nivellos seral de transaminase de acido glutamic oxalacetic e de dishydrogenase lactice esseva facite in 60 patientes inter 12 e 48 horas post le declaration del symptomas initial de acute infarcimento myocardial. Le presentia de tal lesiones esseva corroborate per historias classic in combination con alterationes in series electrocardiographic o per provas necroptic. Omne le patientes monstrava elevate nivellos de transaminase, durante que solmente 35 del 60 habeva etiam elevate nivellos de dishydrogenase lactic. Si un sol test debe esser seligite pro confirmar un impression de acute infarcimento myocardial inter 12 e 48 horas post le declaration del symptomas, le test a transaminase pare esser significativemente superior al test a dishydrogenase lactic.

INHIBITION OF LIPID MOBILIZATION OF SURGICAL STRESS BY PARTIALLY DEPOLYMERIZED HYALURONIC ACID

By Chris J. D. Zarafonetis, M.D.
PROFESSOR OF CLINICAL AND RESEARCH MEDICINE

Joseph Seifter, M.D.
DIRECTOR, WYETH INSTITUTE FOR MEDICAL RESEARCH

David Baeder, Ph.D.
PHARMACOLOGIST, WYETH INSTITUTE FOR MEDICAL RESEARCH

John P. Kalas, M.D.
RESEARCH FELLOW IN MEDICINE

AND

Walter Y. M. Chang, M.D.
RESIDENT, DEPARTMENT OF SURGERY

(From the Departments of Medicine and Surgery, Temple University School of Medicine, Philadelphia, Pennsylvania, and the Wyeth Institute for Medical Research, Radnor, Pennsylvania)

It was demonstrated recently that lipid mobilization occurs in patients as a consequence of surgical stress (Zarafonetis *et al.*[9]). Moreover, evidence was presented which indicated that this effect was mediated through a physiologic mechanism for the acute mobilization of lipids to the liver. The principal elements of this dynamic process may be briefly summarized as follows: In response to caloric requirements induced by the stress of surgery, lipid mobilizer hormone (LM) is released from the posterior pituitary gland into the circulation. LM then causes mobilization of triglycerides from the omentum (and presumably the mesentery) into the portal circulation. Furthermore, paper electrophorograms of omental vein blood samples showed that a marked shift from α-lipoprotein to β-lipoprotein predominance occurred during the course of surgery. The omentum not only responded actively to the endogenous LM with the release of the indicated lipid components but it also appeared to remove some cholesterol from the blood circulating through it. Finally, it was pointed out that any lipid changes observed in the peripheral blood during surgical stress reflected the foregoing events plus the capability of the liver to cope metabolically with the lipid load presented to it.

The purpose of this report is to present observations which indicate that the phenomenon of lipid mobilization may be inhibited by the oral administration of a partially depolymerized hyaluronic acid (PDHA) prior to the subjection of patients to surgical stress. The basis for employing PDHA in this connection stems from a series of investigations by Seifter and Baeder[1-7]. These investigators, working with rats and dogs, demonstrated a lipemia clearing effect with hyaluronidase, with hyaluronate, and with deoxycorticosterone. Furthermore, they showed that the lipemia clearing effect of these substances could be inhibited by the administration of cortisone or by stress (cold exposure), and by nephrosis.

Studies in connection with the latter findings led to the discovery and isolation of LM and its identification as a posterior pituitary hormone[4]. Many laboratory and clinical studies concerning LM have been published (Seifter and Baeder[1-6], Seifter *et al.*[7], Steiger *et al.*[8], Zarafonetis *et al*[9-14]) and need not be reviewed here. They are cited, however, because of the complementary role which the studies on lipid mobilization have for those which deal with inhibition of this response.

The present report, then, is concerned with the inhibition of lipid mobilization by the oral administration of PDHA. This substance was selected in preference to hyaluronidase or deoxycorticosterone because of animal studies which showed it to be effective via the oral route as well as non-toxic in the doses contemplated. The effect of PDHA on the prehepatic and peripherally circulating blood lipids was therefore studied in patients undergoing the stress of surgery. In addition, the concentrations of endogenous plasma LM were determined, and paper electrophoretic analyses of the plasma lipoprotein patterns were made on all of the test specimens. The findings and their inter-relations form the basis of this report.

Materials and Methods. Observations were made on 9 women patients during the course of various intra-abdominal operations at the Temple University Hospital (Table 1). The opportunity presented itself for the study of 2 subjects twice, each through 2 separate intra-abdominal procedures. Thus, in these 2 instances, the patient served as her own control on one occasion, and received PDHA on the other.

TABLE 1.—PATIENTS TREATED WITH PARTIALLY DEPOLYMERIZED HYALURONIC ACID (PDHA) PRIOR TO INDICATED SURGICAL PROCEDURE.

No.	*Patient*	*Age*	*Sex*	*Operation*
1	L. L.	51	F	Proctosigmoidectomy
2	M. G.	44	F	Cholecystectomy
3	H. W.	35	F	Cholecystectomy
4	L. K.	37	F	Cholecystectomy
5	M. H.	41	F	Cholecystectomy
6	L. J.	38	F	Cholecystectomy
7	R. F.	54	F	Excision anus, recto-sigmoid, panhysterectomy
8a	D. F.	33	F	Splenectomy
b*	D. F.	33	F	Cholecystectomy
9a*	K. R.	74	F	Proctosigmoidectomy
b	K. R.	74	F	Excision recurrent sigmoid carcinoma

*Patient D. F. received a placebo instead of PDHA before her second operation, while Patient K. R. received neither placebo nor PDHA during her first operation.

As before[9] complete history, physical examination, and laboratory tests were performed in each case. Records were made of all recent or concurrent chemotherapy or antibiotic administration, of pre-operative medications, anesthetics, and blood or parenteral fluid administration during the operation and the postoperative period. All of the subjects were fasted overnight and through the course of operation and until the post-surgery blood sampling had been completed. In order that the conditions would be identi-

TABLE 2A.—RESULTS OF CHOLESTEROL AND FATTY ACID DETERMINATIONS AND LIPID MOBILIZER ASSAYS IN PATIENTS GIVEN PDHA BEFORE UNDERGOING SURGERY.

Time + Site of Blood Samples		*Determination*	*Case No.* 1	2	3	4	5	6	7	8a	8b*	9a*	9b
Total PDHA Pretreatment (grams)			*0.6*	*0.6*	*0.4*	*0.6*	*2.4*	*1.8*	*0.4*	*3.0*	*0*	*0*	*2.4*
Pre-operative baseline	Ante-cubital vein	Cholesterol mg./100 ml.	240	236	252	212	185	230	242	290	242	222	262
		Fatty Acids mg./100 ml.	290	295	304	284	286	283	384	320	286	238	308
		LM Assay	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
Beginning of operation	Omental Artery	Cholesterol mg./100 ml.	226	250	234	206	182	212	236	212	248	238	236
		Fatty Acids mg./100 ml.	244	250	251	220	120	186	314	134	286	252	312
		LM Assay	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
	Omental Vein	Cholesterol mg./100 ml.	212	234	226	202	182	212	212	210	238	202	218
		Fatty Acids mg./100 ml.	238	242	218	228	118	152	308	130	272	208	308
		LM Assay	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
Time elapsed to next omental specimens			$2\frac{3}{4}$ hr.	$\frac{1}{2}$ hr.	$1\frac{3}{4}$ hr.	2 hr.	2 hr.	$1\frac{3}{4}$ hr.	$4\frac{1}{2}$ hr.	$1\frac{1}{2}$ hr.	$1\frac{1}{2}$ hr.	$3\frac{1}{2}$ hr.	2 hr.
End of operation	Omental Artery	Cholesterol mg./100 ml.	226	240	250	209	184	218	220	214	248	290	208†
		Fatty Acids mg./100 ml.	240	226	212	214	120	148	315	138	302	326	292†
		LM Assay	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.†
	Omental Vein	Cholesterol mg./100 ml.	232	250	246	208	182	201	212	210	236	284	215
		Fatty Acids mg./100 ml.	236	218	218	214	110	150	208	130	560	852	308
		LM Assay	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.
4 hours Post-operative	Ante-cubital vein	Cholesterol mg./100 ml.	228	218	240	210	77	218	236	235	272	299	212
		Fatty Acids mg./100 ml.	236	228	250	210	158	240	224	292	408	372	226
		LM Assay	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.	Pos.

*See footnote, Table 1.
†Radial artery

cal to those of previous studies[9], glucose was omitted from parenteral fluids administered during the test period. The only difference, therefore, was in the administration of PDHA* (partially depolymerized hyaluronic acid) prior to the operation. The material was administered in gelatin capsules, 200 mg. each, usually beginning about 12 hours before surgery. The total dose of PDHA administered prior to surgery varied from 400 to 3,000 mg. The largest doses were given at the beginning of the study. The amount of PDHA was reduced in subsequent patients and still found to be sufficient to achieve the anticipated inhibition of lipid mobilization as previously described[9]. Paper electrophoretic analysis of the plasma specimens for their lipoprotein patterns was also performed in the same manner as before[9].

Results. The cholesterol and fatty acid determinations on the plasma specimens obtained before, during, and after surgery are shown in Table 1 and Tables 2*a*, 2*b*, and 2*c*. The amount of PDHA administered to each subject prior to surgery is given in Table 1 as are the results of the bioassays

TABLE 2B.—PERCENTAGE CHANGES* IN PLASMA CHOLESTEROL AND FATTY ACID VALUES OF PATIENTS STUDIED.

Case No.	*Antecubital Vein*		*Omental Artery*		*Omental Vein*	
	Chol.	*Fatty Acids*	*Chol.*	*Fatty Acids*	*Chol.*	*Fatty Acids*
1	− 5.0%	−18.6%	0%	− 1.6%	+ 9.4%	− 0.8%
2	− 7.6	−22.7	− 4.0	− 9.6	+ 6.8	− 14.0
3	− 4.7	−17.8	+ 6.8	−15.5	+ 8.8	0
4	− 1.0	−26.1	+ 1.5	− 2.7	+ 2.9	− 6.1
5	−58.8	−45.1	+ 1.1	0	0	− 6.8
6	− 5.1	−15.2	+ 2.8	−20.4	− 5.2	− 1.3
7	− 2.5	−41.7	− 6.8	+ 0.3	0	− 32.5
8a	−18.9	− 8.8	+ 1.0	+ 3.0	0	0
8b*	+12.4	+42.6	0	+ 5.6	− 0.8	+105.9
9a*	+34.7	+56.3	+19.3	+29.4	+40.6	+309.6
9b	−19.1	−26.6	− 9.0	− 6.4	− 1.4	0
Average	−13.6%	−24.7%	− 0.7%	− 5.9%	− 2.3%	− 6.8%

*Calculated from data in Table 2a. Data during "control" operations (8b and 9a) excluded from averages.

in doses of about 10 mg. per kg. of body weight. Lesser amounts were not tested. One of the 2 patients who underwent 2 separate operations was given 600 mg. $CaCO_3$ in identical capsules as a placebo during the second operation. The other received no placebo during the first operation (Case 3, Table 2, Ref. 9), and was given 2.4 gm. PDHA prior to the second procedure.

Blood specimens were collected from the antecubital vein before and 4 hours after operation, and from branches of the omental artery and omental vein at the beginning and at the end of the abdominal phase of the procedure.

All of the blood specimens were analyzed for cholesterol and total fatty acids and were assayed for lipid mobilizer hormone activity of each plasma sample for lipid mobilizer hormone. In addition, the findings in 2 patients (8*b* and 9*a*) who were not pretreated with PDHA on the occasion of a second operation are shown for comparison. Results in 2 individual cases are presented in Figs. 1*a* and *b* and Figs. 2*a* and *b*.

1. EFFECT OF PDHA ON PLASMA LM CONTENT DURING STRESS OF SURGICAL PROCEDURE. In every case the assays for LM were negative in tests on the baseline antecubital vein blood specimens, and on the omental arterial and venous

*Prepared at the Wyeth Institute for Medical Research, Radnor, Pa., Code No. Wy-2077.

blood samples taken at the beginning of the intra-abdominal phase of the operation. All of the blood specimens taken at the end of surgery or 4 hours after the operation, on the other hand, gave positive reactions for the presence of increased concentrations of circulating LM. These findings are similar to those observed in subjects who did not have prior treatment with PDHA (for example, patients 8*b* and 9*a*, and those in Reference 9). Pre-treatment with PDHA, therefore, did not prevent the release of endogenous LM during the course of surgery.

2. EFFECTS OF PDHA ON PLASMA LIPID CHANGES DURING STRESS OF SURGERY.

a. *Antecubital vein blood.* The post-operative plasma cholesterol values decreased an average of 13.6% (range −1.0% to −58.8%) from the base-line pre-operative findings. At the same time, fatty acid values declined an average of 24.7% (range −8.8% to −45.1%).

b. *Omental artery blood.* The changes which occurred in the plasma cholesterol and fatty acids of the omental arterial blood samples are given in Tables 2*a*, *b*, and *c*. There were some that showed minor increases and others whose values decreased somewhat during surgery. The resultant averages, therefore, indicated a decline of only 0.7% (range +6.8% to −9.0%) in the plasma cholesterol concentration, while the average for change in fatty acid values was −5.9% (range +3.0% to −20.4%).

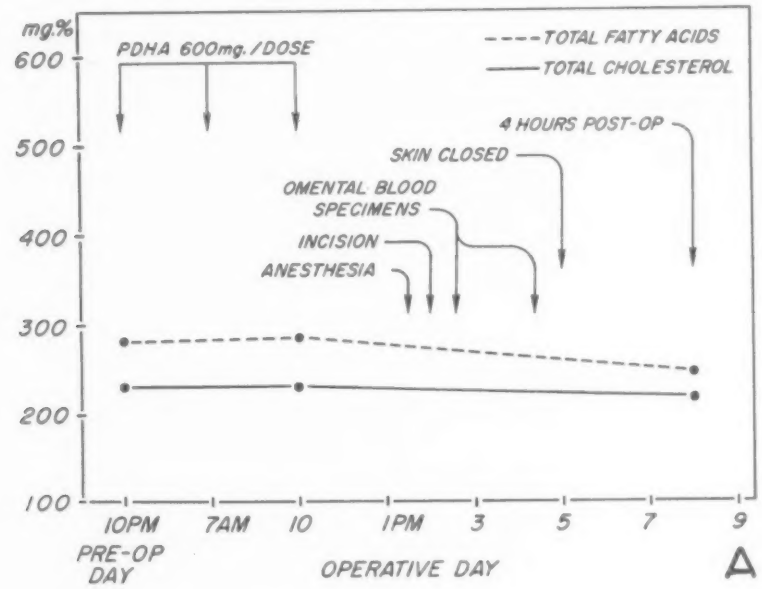
c. *Omental vein blood.* Here, too, there were small fluctuations with the notable exception of case 7, whose fatty acid concentration decreased 32.5%. The average for cholesterol values, however, was only 2.3% lower than for the early operation specimens, and the average for fatty acids was −6.8%.

d. *Arteriovenous differences of cholesterol values.* In Table 2*c* are shown

TABLE 2*C*.—ARTERIOVENOUS DIFFERENCES* IN PLASMA CHOLESTEROL AND FATTY ACID VALUES BETWEEN OMENTAL ARTERY AND OMENTAL VEIN AT BEGINNING AND END OF INTRA-ABDOMINAL PROCEDURES

	Cholesterol—difference in mg. per 100 ml.		*Fatty Acids—difference in mg. per 100 ml.*	
Case	*Begin. oper.*	*End oper.*	*Begin. oper.*	*End oper.*
1	−14	+ 6	− 6	− 4
2	−16	+10	− 8	− 8
3	− 8	− 4	−33	+ 6
4	− 4	− 1	+ 8	0
5	0	− 2	− 2	− 10
6	0	−17	−34	+ 2
7	−24	− 8	− 6	−107
8a	− 2	− 4	− 4	− 8
8b	−10	−12	−14	+258
9a	−36	− 6	−44	+526
9b	−18	+ 7	− 4	+ 16
Average†	−9.6	−1.4	−9.9	−12.6

*Calculated from data in Table 2a.
†Averages are exclusive of findings in 8b and 9a during "control" operation



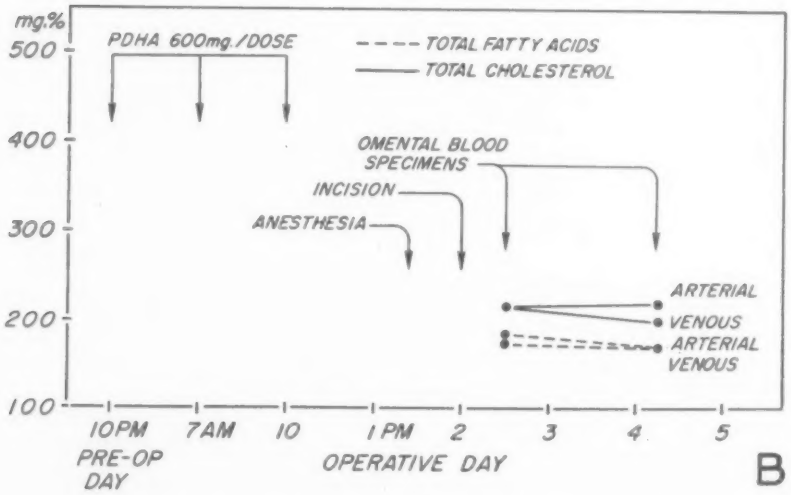


Fig. 1*a*.—Plasma lipid values (antecubital vein blood) of patient, L.J., a 38-year-old Negro woman, before and after cholecystectomy. She had been given a total of 1.8 gm. PDHA, orally, during the preceding 15 hours. Note the insignificant change in the post-operation peripheral lipid values.

Fig. 1*b*.—Plasma lipid values of omental artery and omental vein blood specimens taken at indicated times from same patient. Note the lack of increase of the fatty acids in pre-hepatic blood obtained from the omental vein late in surgery. (This is in contrast to the marked increase in plasma fatty acids in other patients under similar conditions but who were not pretreated with PDHA[9].)

the differences between the omental arterial and venous cholesterol values at the beginning and at the end of the intra-abdominal operations. The differences are very slight and insignificant.

e. *Arteriovenous differences of fatty acid values.* At the beginning of the operation, the average value for triglycerides was 9.9 mg. per 100 ml. less in the venous specimens than was found in the arterial samples. By the

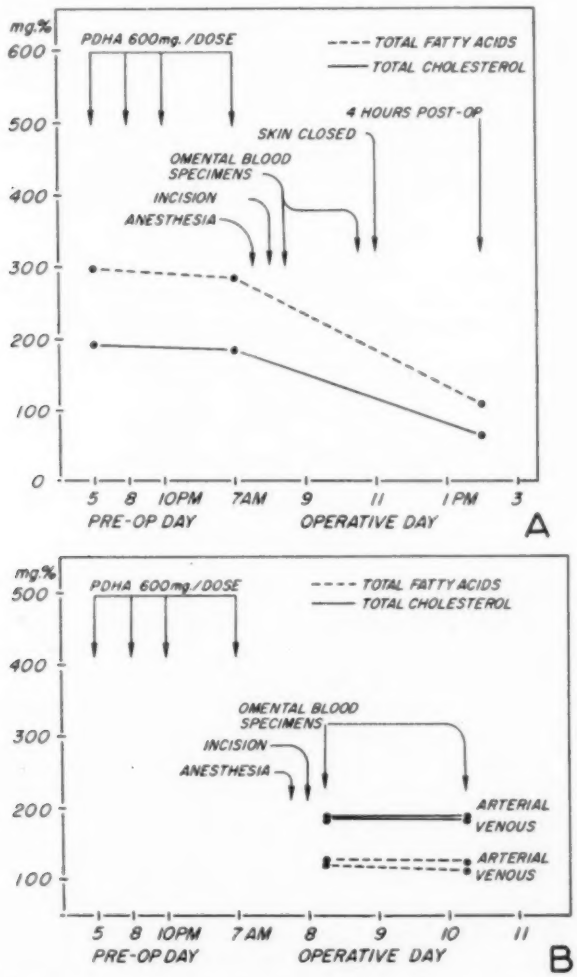


Fig. 2*a*.—Plasma lipid values (antecubital vein blood) of M.H., a 41-year-old Negro woman, before and after cholecystectomy. This patient was pretreated with 2.4 gm. PDHA. Note the definite decline in the cholesterol and fatty acid content of the peripheral blood specimen drawn 4 hours after the operation.

Fig. 2*b*.—The plasma lipid values for the indicated omental blood specimens from patient, M.H., are shown. Note particularly the lack of increase in the pre-hepatic fatty acids of the late omental vein sample over the early, base-line value.

end of the procedures, the average difference was 12.6 mg. per 100 ml. less on the venous side. Except for case 7 (Table 2*c*), whose fatty acid level fell 107 mg. per 100 ml., the remaining subjects exhibited minor fluctuations. These findings are in marked contrast to those observed in patients who did not receive PDHA before surgery; for example, case 8*b* and 9*a* (Table 2*c*). In these 2 instances, the omental vein fatty acids were 256 mg. and 526 mg. per 100 ml. greater, respectively, than the values for omental arterial blood drawn at the same time.

in circulating endogenous lipid mobilizer hormone uniformly occurred during the course of surgery is evident from the bioassay results shown in Table 1. This was to be expected in view of similar findings in another group of patients studied under comparable conditions[9]. However, the increase in plasma LM was not followed by an outpouring of fatty acids into the pre-hepatic circulation as was uniformly exhibited by patients who were not pre-treated with partially depolymerized hyaluronic acid. Thus, PDHA did not prevent the release of LM from

TABLE 3.—PERCENTAGE CHANGES DURING STRESS OF SURGERY IN PLASMA CHOLESTEROL AND FATTY ACID VALUES OF PDHA TREATED PATIENTS COMPARED WITH FINDINGS IN NON-PDHA TREATED SUBJECTS OF PREVIOUS STUDY.*

	Antecubital Vein		*Omental Artery*		*Omental Vein*	
	Chol.	*Fatty Acids*	*Chol.*	*Fatty Acids*	*Chol.*	*Fatty Acids*
No PDHA* (avg. 11 cases)	+26.3%	+41.5%	+8.1%	+20.9%	+10.9%	+122%
PDHA (avg. 9 cases)	−13.6%	−24.7%	−0.7%	− 5.9%	− 2.3%	− 6.8%

*Reference 9.

3. EFFECT OF PDHA ON ELECTROPHORETIC PATTERN OF PLASMA LIPOPROTEINS DURING STRESS OF SURGERY. Paper electrophoretic analysis of the lipoproteins was performed on all of the plasma specimens from these patients. In contrast to the striking shift from α-lipoprotein to β-lipoprotein predominance which was observed uniformly in the omental vein blood specimens of non-PDHA treated subjects[9], none of the patients in this group who were given PDHA showed any significant alteration of the plasma lipoprotein pattern during the course of surgery. In Fig. 3*a*, *b*, and *c* are shown the paper electrophoretic patterns obtained in one of the PDHA treated patients. The depicted findings are typical for the entire group.

Discussion. That a marked increase

the posterior pituitary, but did apparently prevent the effect of LM at the omental level. The effectiveness of PDHA in preventing lipid mobilization from the omental depot is clearly demonstrated in Table 3. Here the average findings of the present group of PDHA pretreated subjects are contrasted with the average changes observed in the non-PDHA patients who had undergone similar surgical procedures[9]. Generally, the plasma cholesterol and fatty acid values increased in the non-PDHA group, with the most dramatic increase of 122% being noted in the fatty acids of the omental vein blood. The PDHA group, on the other hand, tended to develop lower levels of these plasma lipid components. It would seem, therefore, that not only was there no mobilization of lipids in

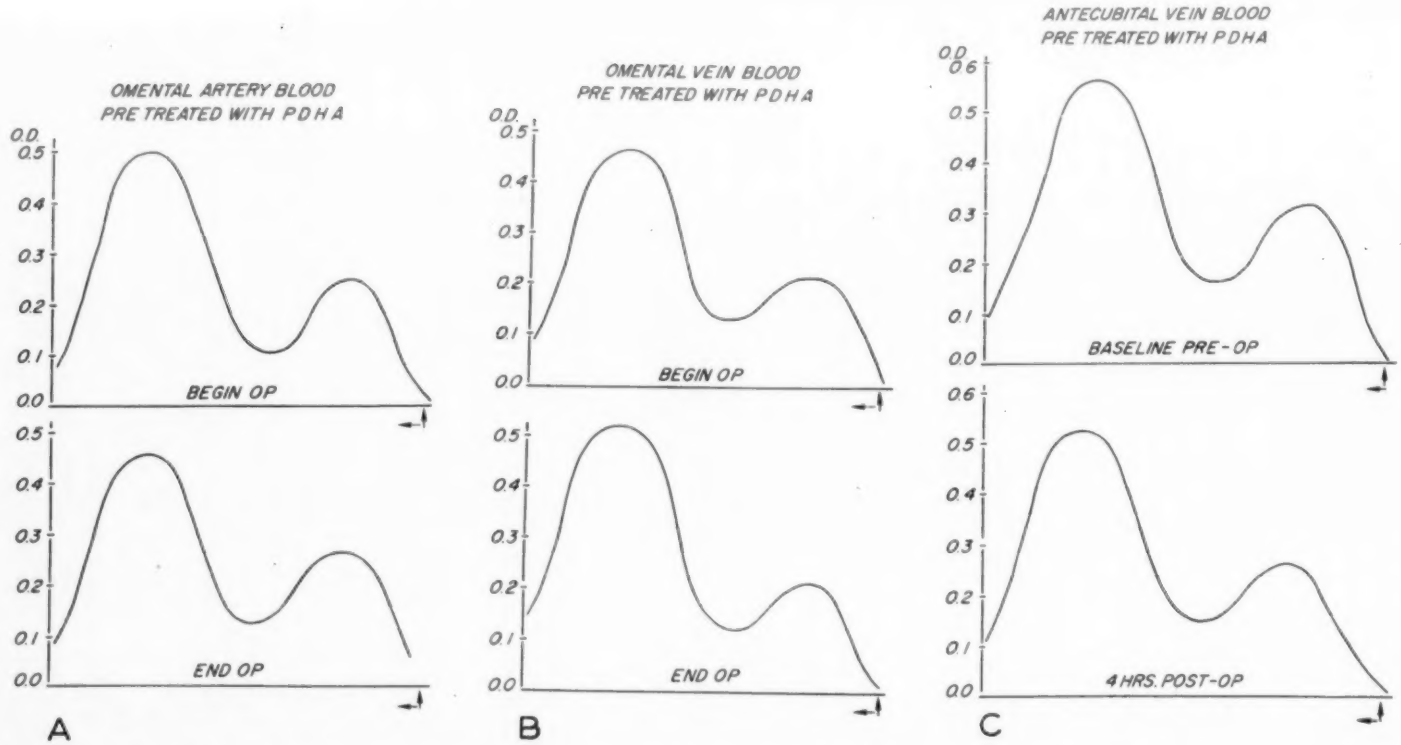


Fig. 3*a*, *b* and *c*.—Paper electrophoretic patterns of plasma lipoproteins of patient, L.J., before, during and after cholecystectomy. As can be seen, there was no significant change of the lipoprotein patterns of the specimens from omental artery, omental vein, or antecubital vein. (This is in contrast to the marked shift from α-lipoprotein to β-lipoprotein predominance in the late omental vein specimens obtained from patients who did not receive PDHA prior to operation[9].)

this group, but metabolic utilization of lipids also appeared to continue during the period of observation.

Of interest, moreover, was the finding that pre-treatment with PDHA prevented the acute changes in lipoprotein patterns as determined by paper electrophoresis. It will be recalled that the pre-hepatic blood specimens from non-PDHA treated subjects showed a marked shift from α-lipoprotein to β-lipoprotein predominance in patterns obtained by this technique[9].

The mode of action of PDHA in preventing the omental (and presumably mesenteric) fat depot from responding to the lipid mobilizer hormone is not known at present.

There were no untoward clinical effects encountered in these patients. PDHA did not display any anticoagulant action.

In view of its apparent non-toxicity, and its striking ability to block the effect of the lipid mobilizer hormone at the omental level, it is possible that PDHA may have important clinical implications for both acute and chronic hyperlipemic states. Studies are currently in progress, therefore, to determine the effect that long term administration of PDHA may have in patients with familial lipid dyscrasias[15].

Summary. A partially depolymerized hyaluronic acid (PDHA) was administered orally in doses of from 400 to 3,000 mg. to 9 patients prior to intra-abdominal surgery. Although increased amounts of lipid mobilizer hormone (LM) were released into the blood of all of these patients during the course of surgery, lipid mobilization from the omental depot did not follow. PDHA, therefore, appeared to block the effect of LM at the omentum.

There were no untoward effects attributed to PDHA, which may hold important clinical implications for both acute and chronic hyperlipemic states.

ADDENDUM: Seifter and Baeder (Fed. Proc., *18*, 443, 1959) recently reported that the oral administration of 5 mg. PDHA per kg. completely blocked the action of LM injected into fasted intact, adrenalectomized or hypophysectomized rats.

ACKNOWLEDGMENTS: The authors wish to express their gratitude to Elizabeth Moses, Faye Baldwin, and Mary Lou Snodgrass at the Temple University Hospital, and W. H. Bechman, J. Dachiw, Joan Howitz, Joseph DeGrazia, Robert Panasevich and E. E. Livingston, Jr. at the Wyeth Institute for Medical Research, Radnor, Pa., who provided invaluable technical assistance throughout the course of this study.

REFERENCES

1. **Seifter, J., and Baeder, D. H.:** Proc. Soc. Exper. Biol. & Med., **86**, 709, 1954.
2. Iidem: Ibid., **91**, 42, 1956.
3. Iidem: Ibid., **93**, 63, 1956.
4. Iidem: Ibid., **95**, 318, 1957.
5. Iidem: Ibid., **95**, 469, 1957.
6. Iidem: Ibid., **95**, 747, 1957.
7. **Seifter, J., Baeder, D. H., Zarafonetis, C. J. D., and Kalas, J.:** *in* Hormones and Atherosclerosis. Edited by **G. Pincus.** New York: Academic Press, Inc., 1959.
8. **Steiger, W. A., Zarafonetis, C. J. D., Miller, G. M., Seifter, J., and Baeder, D. H.:** Am. J. Med. Sci., **232**, 605, 1956.
9. **Zarafonetis, C. J. D., Seifter, J., Baeder, D. H., and Kalas, J. P.:** Ibid. **237**, 418, 1959.
10. **Zarafonetis, C. J. D., Miller, G. M., Steiger, W. A., Seifter, J., Baeder, D. H., and Myerson, R. M.:** Abstr., J. Lab. & Clin. Med., **48**, 961, 1956.
11. **Zarafonetis, C. J. D., Miller, G. M., Seifter, J., Baeder, D. H., Myerson, R. M., and Steiger, W. A.:** Am. J. Med. Sci., **234**, 493, 1957.
12. **Zarafonetis, C. J. D., Miller, G. M., Seifter, J., and Baeder, D. H.:** Ibid., **235**, 410, 1958.
13. **Zarafonetis, C. J. D., Seifter, J., Baeder, D. H., and Kalas, J. P.:** Abstr., J. Lab. & Clin. Med., **50**, 965, 1957.
14. Iidem: Abstr., Clin. Res., **6**, 265, 1958.
15. Iidem: To be published.

(Interlingua on page 748)

PROGRESS
OF
MEDICAL SCIENCE

PEDIATRICS

UNDER THE CHARGE OF

IRVING J. WOLMAN, M.D.
DIRECTOR OF LABORATORIES, CHILDREN'S HOSPITAL OF PHILADELPHIA
PROFESSOR OF PEDIATRICS, UNIVERSITY OF PENNSYLVANIA

AND

ALFRED M. BONGIOVANNI, M.D.
DIRECTOR, ENDOCRINE DIVISION, CHILDREN'S HOSPITAL OF PHILADELPHIA
ASSOCIATE PROFESSOR OF PEDIATRICS, UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PENNSYLVANIA

NEONATAL HEMATOPOIESIS: A COMMENTARY

BY ROBERT D. GENS, M.D.

(From The Children's Hospital of Philadelphia and the Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania)

THE hematologist does not deal with such profound changes in newborn physiology as occur in the province of cardiologists and respiratory physiologists, but the alterations in oxygen availability, and the changes in blood volume which accompany delivery do affect an infant's hematopoietic future. These alterations are not in themselves entirely responsible for the changes in hematopoiesis observed in the newborn, and many of the phenomena of newborn hematopoiesis still require explanation. As in the other organ systems of the infant, the hematopoietic system of the newborn undergoes alterations which assist in the adaptations to extrauterine life. A summary of these alterations is the purpose of this report. Table 1 is a compilation of average peripheral blood values, prepared from 6 authoritative sources.

TABLE 1.—MEAN PERIPHERAL BLOOD VALUES DURING THE NEONATAL PERIOD*

Age	*Hemoglobin* Gm. %	*Erythrocytes* cells/c.mm.	*Leukocytes* cells/c.mm.	*Granulocytes* %	*Platelets* /c.mm.	*Reticulocytes* %
Birth	19.8	5,100,000	24,000	69	227,000	3.40
1 week	16.3	5,300,000	10,600	45	233,000	0.17
2 weeks	16.5	5,000,000	11,000	26	242,000	0.21
3 weeks	16.0	4,600,000	10,500	30	269,000	0.14
4 weeks	15.5	4,500,000	10,000	31	277,000	0.10

*Average of data, ref.[11,13,14,16,24,25]

ERYTHROPOIETIC SYSTEM. Of all the formed elements of the blood, the erythrocyte and its precursors have been the most completely studied. A recent article[7] excellently summarizes the correlations of the hemoglobin level, erythrocyte count, reticulocyte count, hematocrit, and cell indices with age during infancy. These values are predicated in part on certain phenomena which must be considered in the interpretation of data from an individual infant. One of the most important variables, so far as hemoglobin values are concerned (and there is no reason to doubt that this generalization does not extend to the erythrocyte count and hematocrit), is the method of collection[17]. The concentration of hemoglobin in capillary blood during the first several days of life is, on the average, 3.6 gm.% higher than venous blood. Another variable is the timing of cord ligation. De Marsh, Act and Wendel[5] have noted that the average erythrocyte count of 1-day-old newborn infants whose cords were clamped late was about 500,000 per c.mm. higher than the counts from a comparable group of infants whose cords were clamped early. Lastly, the birth weight of the infant is probably of importance since it has been shown that premature infant's erythrocyte counts are dissimilar from full term infant's counts[14]. The direction of this dissimilarity is inconstant. Some authors report higher counts in premature infants than in full term infants and other authors have made a contrary observation[4,6,23,24]. There appear to be no reports of data on the erythrocyte counts and hemoglobin levels of postmature infants; yet these data would be of interest since placental insufficiency probably produces a decrease in the oxygen saturation of fetal blood.

The influence of the variables just mentioned on the normal blood values of the newborn has not been completely elucidated; however, certain changes in these values deserve comment. Studies reporting frequent serial hematological examinations leave little doubt that the erythrocyte count rises slightly during the first day and then declines, slowly at first, and then more rapidly, during the remainder of the neonatal period. The hemoglobin level also increases slightly during the first day of life, followed by little change until about the fourth or fifth day when a slow decline begins. The hematocrit similarly rises during the first day of life, and then falls throughout the remainder of the neonatal period. Reticulocytes and nucleated red blood cells are fairly frequent in the peripheral blood of newborn infants and most abundant in premature infants. By the end of the first week, nucleated red blood cells have practically disappeared from the peripheral blood, and the reticulocyte count has assumed the level seen in older children. The reticulocyte count appears to decline further during the remainder of the neonatal period. Newborn erythrocytes are large, the mean corpuscular volume being 113 cubic microns; this value declines during the neonatal period and the mean corpuscular hemoglobin follows a similar pattern. The mean corpuscular hemoglobin concentration, however, rises during the neonatal period. The survival of newborn erythrocytes has been studied by Mollison[15] utilizing the Ashby technique, and the indications are that their survival is shorter than that of adult erythrocytes.

It would seem, then, that the infant when born is briskly manufacturing macrocytic erythrocytes. This aggressive production of erythrocytes is rapidly curbed during the early days of life, to be followed by the appearance of small cells in the circulation. Whether these small cells can claim

the macrocytes just described as their predecessors or whether they arise directly from normoblasts is not clear. From about the fifth or seventh day to the end of the first month the production of erythrocytes and hemoglobin is not sufficient to parallel the growth of the infant's blood volume and the count per unit volume drops as a result.

One further comment seems necessary. Most of the data used for the determination of normal newborn hematologic values were compiled in an era when the prevalence of maternal-fetal erythrocyte incompatibility (particularly ABO incompatibility) was not appreciated. Future studies of normal newborn erythrocyte values should exclude patients who exhibit the possibility of these incompatibilities.

LEUKOCYTIC SYSTEM. It is in reference to the leukocytic system that one is most hesitant to apply the term normal. Substantial data[21,22,26] indicate that the total leukocyte count is high at birth and begins to decline about the fourth day. During these early days a range of values from 4,000 per c.mm. to 43,000 per c.mm. is shown by infants who have no demonstrable disease process. Further, there is no evidence to indicate that there are alterations in the leukocyte count in response to time of day, food, body activity or birth trauma[11]. The neutrophilic series makes up about 75% of the total leukocyte count during the first several days, and from 20 to 40% of these neutrophils may be nonsegmented forms. The decline of the leukocyte count after the fourth day results mainly from a decrease in the neutrophil percentage, so that by the eighth day the neutrophils represent some 45% of the total leukocyte population.

It is difficult to accept that a leukocyte count can vary widely in a newborn without these variations being indicative of a reaction to some stimulus. Hypoxemia probably is not involved, since in adults exposed to high altitudes the leukocyte counts remain relatively unchanged[20]. Exposure to subclinical infections may explain a leukocytosis in some infants but would probably not account for the leukocytosis noted in the cord blood. It is not unreasonable to postulate that the occurrence of an increase in numbers of young neutrophils may represent a response to a maternal fetal incompatibility with respect to white cell antigens, since it has been shown that multiple transfusions are associated with the production of leukocyte antibodies[2,10,12], and that nontransfused multiparous women occasionally exhibit leukocyte antibodies[18].

THROMBOCYTIC SYSTEM. The variation in the platelet count of the newborn appears to be great. This variation may be attributed in part to differences in technique between various clinics and to the variability of the platelet count itself among different individuals when the same technique is utilized. Some of this difficulty has been resolved recently by the demonstration[1] that although the platelet count may vary between individuals (adults were used in this study) the platelet count of an individual remains remarkably constant during repeated observations. Serial observations[13] indicate that the platelet count rises slightly during the neonatal period and that the platelet count in premature infants increases in the same manner but begins at a lower value. Thrombocytosis has been reported[3] in infants subjected to trauma or asphyxia, and thrombocytopenia has been recorded[9] in infants born to normal mothers. The mechanism of this thrombocytopenia is presumed to be a dissimilarity of maternal and fetal platelet antigens, with subsequent isoim-

munization and sensitization in a manner analogous to erythroblastosis fetalis.

CONCLUDING COMMENT. The disease processes which may affect the newborn hemopoietic system are varied, and many of these processes are not found outside of the neonatal period. The laboratory recognition of these disease processes depends not only on the array of normal values as correlated with age but also on an awareness of the factors which are operative in producing alterations in blood values during the neonatal period.

REFERENCES

(1) **Brecher, M.,** and **Cronkite, J.:** App. Physiol., **3,** 365, 1950. (2) **Brittingham, T. E.:** Vox sang., **2,** 242, 1957.
(3) **Celautano, P.:** Arch di ostet. e ginec., **57,** 113, 1952. (4) **Chuinard, E. G., Osgood, E. E.,** and **Ellis, D. M.:** Am. J. Dis. Child., **62,** 1188, 1941.
(5) **DeMarsh, Q. B., Act, H. L.,** and **Wendel, W. F.:** J. Am. Med. Assn., **116,** 2568, 1941.
(6) **Findlay, L.:** Arch. Dis. Child., **21,** 195, 1946.
(7) **Guest, G. M., Brown, E. W.,** and **Lahey, M. E.:** Pediat. Clin. N. America, 357, 1957. (8) **Guest, G. M., Brown, E. W.,** and **Wing, M.:** Am. J. Dis. Child., **56,** 529, 1938.
(9) **Harrington, W. J.:** Ann. Int. Med., **38,** 433, 1953.
(10) **Killman, S. A.:** Danish Med. Bull., **5,** 178, 1958.
(11) **Lippman, H. S.:** Am. J. Dis. Child., **27,** 473, 1924. (12) **Loghem, J. J., Jr., Van der Hart, M., Hijmans, W.,** and **Schmit, H. R.:** Vox sang., **3,** 203, 1958.
(13) **Merritt, K. K.,** and **Davidson, L. T.:** Am. J. Dis. Child., **46,** 991, 1933. (14) Iidem: Ibid., **47,** 261, 1934. (15) **Mollison, P. L.:** Lancet, **1,** 513, 1948.
(16) **Nelson, W. E.:** Textbook of Pediatrics, 6th ed. Philadelphia: W. B. Saunders Co., 1954.
(17) **Oetlinger, L.,** and **Mills, W. B.:** J. Pediat., **35,** 362, 1949. (18) **Payne, R.,** and **Rolfs, M. R.:** J. Clin. Invest., **37,** 1756, 1958.
(19) **Smith, C. A.:** The Physiology of the Newborn Infant. 2nd ed. Springfield, Ill.: Charles C Thomas, 1953.
(20) **Talbott, J. H.:** Folia hemat., **55,** 23, 1936.
(21) **Washburn, A. H.:** Am. J. Dis. Child., **47,** 993, 1934. (22) Idem: Ibid., **50,** 395, 1935. (23) **Waugh, T. R., Merchant, F. T.,** and **Maughan, G. B.:** Am. J. Med. Sci., **198,** 646, 1939. (24) **Wegelius, R.:** Acta pediat. Supp., 4, 1, 1948. (25) **Wintrobe, M.:** Clinical Hematology, 4th ed. Philadelphia: Lea & Febiger, 1956. (26) **Wollstein, M.:** Handbook of Hematology, edited by **H. Downey.** New York: Paul B. Hoeber, Inc., **2,** 923, 1938. (27) **Wolman, I. J.:** Laboratory Application in Clinical Pediatrics. New York: McGraw-Hill Book Co., 1957.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

CARL BACHMAN, M.D.
PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PENNSYLVANIA

AND

FRANKLIN L. PAYNE, M.D.
PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE
UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PENNSYLVANIA

BACTEREMIC SHOCK IN OBSTETRICS

BY W. Z. BRADFORD, JR., M.D.
INSTRUCTOR IN OBSTETRICS AND GYNECOLOGY

AND

CARL BACHMAN, M.D.
PROFESSOR OF OBSTETRICS AND GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PENNSYLVANIA

OVERWHELMING puerperal septicemia, the *sepsis foudroyante* of the French, has been observed only very rarely since the advent of the sulfonamide and antibiotic era. In view of this, the fact that 20 such cases, resulting in 9 maternal deaths, should have been noted during the past 3 years is of more than passing interest (Table 1).

GENERAL CASE DATA. Without exception, all of the recently observed cases have been examples of acute bacteremic shock caused by Gram-negative organisms. *Escherichia coli* was demonstrated or presumed to be the infective agent in 17 instances, and *Pseudomonas aeruginosa* in 3. No Welch bacillus or antibiotic-resistant staphylococcal infections were encountered in the group [4,9,16,22,30,31,32].

TABLE 1.—SEPTIC OBSTETRIC SHOCK

	Escherichia coli Infections	*Pseudomonas aeruginosa* Infections
Total cases	17*	3
First trimester	(3)	(1)
Second	(11)	(0)
Third	(3)*	(2)
Postive cultures	14*	3
Maternal deaths	9	0
Reference numbers	4, 9, 31, 32	22, 30

*Includes one infection introduced by a contaminated blood transfusion.

Excluding one patient whose infection was accidentally introduced by an infusion of bank blood contaminated with a cold-growing colon bacillus[9], all infections were of primary genital origin. Of the 19 cases of this type, 4

occurred during the course of prolonged labor at or near term; in all of these, the amniotic membranes had ruptured (or been punctured) prior to the onset of labor, and the bacteremia presumably resulted from an ascending trans-vaginal contamination and infection of the uterine contents; the infecting organism was *E. coli* in 2 cases, and *Ps. aeruginosa* in 2; although all the mothers recovered, none of the fetuses or infants survived[9,22,30]. The remaining 15 infections represented complications of abortions occurring, in most instances, during the early weeks of the second trimester; the infective organism was proven or believed to be *B. coli* in 14 cases, and *Ps. aeruginosa* in 1; of these 15 patients, 9 died, all deaths being in the group of second-trimester abortions[4,9,30,31,32].

CLINICAL FEATURES. Review of the case-protocols of the reported infections permits the following generalizations.

The initial clinical course follows a consistent pattern regardless of the maturity of the pregnancy at which abortion or labor may occur. Fever appears after some hours of uterine contractile activity; it usually is ushered in by chilliness or rigor, but is often deceptively moderate in height and remittancy. During this early febrile phase, the patient remains alert and relatively free of symptoms of general toxicity, and of significant local signs of developing inflammatory lesions of the pelvic organs or peritoneum. The skin is flushed and warm, the pulse moderately elevated but full and bounding, and the leukocyte count normal or slightly depressed with respect to the number of neutrophils.

Shock develops at the end of intervals varying between 8 and 36 hours following the onset of fever. Its development may be insidious and (since overt or concealed hemorrhage is usually absent) may be unsuspected, unless the blood pressure levels and current rates of urinary excretion are checked at regular intervals. However, the full flowering of the classical symptoms of acute shock is never long delayed. In general, these symptoms appear prior to the completion of the labor or abortion, and in spite of vigorous interim antibiotic therapy. In abortions, moreover, such therapy may be partially ineffective for the reason that spontaneous evacuation of the uterus is apt to be delayed or incomplete, leaving a residuum of semi-detached but imprisoned, devitalized and infected secundines beyond the reach of any systemically administered antibiotics.

The onset of shock is accompanied by the appearance of a moderate cyanosis and by oliguria or anuria, with the urine remaining free of albumin during the early phases. Efforts to combat it by intravenous infusions of blood or plasma-expanders are generally ineffective, and may provoke the development of pulmonary edema unless the infusions are limited to such volumes as may be necessary for the treatment of dehydration or blood loss. Apart from adequate and judiciously selected antibiotic therapy, the most effective measures are two-fold. One is the aggressive employment of such vasoconstrictors as levarterenol or metraminol. The other is the prompt instrumental evacuation of any retained secundines, or, if this be not feasible *per vaginam*, prompt resort to hysterectomy.

Unless the shock can be relieved within a matter of hours, it becomes irreversible and the patient dies. When death occurs, it generally does so within 24 hours of the onset of the shock, and is attended by terminal manifestations of pulmonary edema

Where treatment of the shock is effective, recovery is the rule, though several days may be required for full restoration of renal function. Probably because of the youthful age of these patients, late death following recovery from shock, and due to irreversible renal failure or other complications, are not likely to be encountered (1 case only).

PATHOLOGICAL DATA. The surgical and postmortem pathological features have been studied in detail by Studdiford and Douglas[31].

In severe cases, the placentas are devitalized, and the blood vessels of the chorionic villi are distended with Gram-negative bacteria. There is no inflammatory reaction to these bacteria in the stroma of the villi. Similarly, no reaction is observed in the underlying decidua unless the organisms have gained access to the intervillous spaces. Such reaction, however, is uniformly present in the decidua and myometrium in cases in which the placenta has been passed, but no pathological pelvic or peritoneal findings are to be noted outside of the placental site.

In postmortem material, no major foci of infection are to be found outside of the uterus, nor is there any evidence of cardiac disease. The lungs are markedly edematous grossly, and microscopic examination reveals the presence of fluid in the alveoli. The liver shows varying degrees of passive congestion, but is otherwise essentially normal. The kidneys reveal dilatation and engorgement of the glomerular vessels, and degenerative changes in the tubules, particularly in the proximal convoluted portions. Hemorrhage into the adrenals was noted in only 2 cases[1,31].

COMMENT. To those familiar with bacteremic shock, it will be apparent that the cases here reviewed represent obstetrical examples of a problem that has been receiving increasing attention during recent years in other fields of clinical medicine and in the basic sciences. The problem has, indeed, a much older background, for it has intrigued clinicians and physiologists at least since the days of Laennec. The essential nature of the principal hemodynamic disturbance was already appreciated more than 50 years ago by Romberg and his associates[25], and by Janeway[15].

No attempt need be made here, therefore, to review the general background literature of this field. Access to the principal clinical reports of recent years may be found in the papers of Hall and Gold[13], and in other contributions[1,5,12,17,19,28,37,38,42,43]. Similarly, access to the results of investigative studies of the circulatory difficulties attending such shock, may be found in reviews of this area by Thomas[33,34], and in other cited references[2,3,6,7,10,11,14,18,20,21,24,26,27,29,35,36,39,40,41,44].

Although no clinical investigation of hemodynamic alterations in bacteremic shock has thus far been made among obstetrical patients, there is no reason to believe that they differ materially in nature or pathogenesis from those seen in non-obstetrical patients. Thus, hypovolemia can hardly be an important underlying factor in the shock, if only because hemorrhage and dehydration are usually absent or minimal in most obstetrical examples of this condition. It would appear that the initial disturbance may consist of pooling of a part of the circulating blood in the portal-splanchnic venous bed, and that the effect of this is to diminish venous return to the heart, with consequent lowering of cardiac output. This phenomenon occurs very promptly when bacterial endotoxin is injected into experimental animals; it appears to be due to a direct vasoconstrictor effect of the toxin upon

hepatic venules. The initial effects of this phenomenon upon the circulation are shortly supplemented by manifestations of widespread peripheral venous stasis, believed to result from further action of the endotoxin upon central sympathetic nerve centers. The circulatory collapse produced by these complex factors is profound and difficult to combat. Toxic effects upon other tissues have also been described, but it seems probable that more serious effects are apt to be sustained by the myocardium, kidneys and other parenchymatous organs as a result of protracted general hypoxia attending the state of shock than from endotoxic tissue damage. The need to combat the symptoms of shock is therefore as urgent as the simultaneous need to attack the underlying infection.

Comparison of the obstetrical cases of bacteremic shock under review with those encountered in other fields of medicine leaves small room for doubt that the former are considerably more acute and fatal. This is manifest not only in the fulminating nature of the clinical phenomena, but also in the mortality data. The deaths in these cases must be viewed in the light of the patients' youthful ages, and of the speed with which the deaths occurred. In comparable series of cases observed in non-obstetrical patients, bacteremic shock has rarely been encountered in modern times among young patients. The average age is in the range of 50 years, and the average age of the fatal cases is higher than this. Although the case-mortality rate in some of the elderly age groups may be high, a significant number of deaths among patients of advanced age occur as a result of late renal and other complications following recovery from shock. On the other hand, all but one of the reported obstetrical deaths occurred within 24 hours of the appearance of hypotension.

The acuity and fulminating nature of the toxic process in septic obstetrical shock are in striking contrast to the minimal nature of the associated local inflammatory processes in the tissues. In no comparable instances of such shock seen in medical and surgical infections is this disparity so apparent, except probably in those cases arising from localized prostatic and other urological foci of infection among elderly male patients. In the abortions observed among the reported obstetrical cases of shock, a prior history of efforts to procure abortion by illegal means was sometimes elicited. But in no instance was any uterine perforation or other evidence of serious local tissue trauma manifested. The limited extent and severity of the uterine inflammatory findings has already been noted in the section on pathologic data above. The significance of the "placental bacteremia" described by Studdiford[31] probably lies in the fact that it indicates the presence of a large accumulation of bacteria in a location not readily affected by antibiotics, once ovular death has occurred. Fundamentally, the placenta represents a membrane estimated to be 7 square meters in area at term. Under these circumstances it is probably capable of inundating the maternal blood with the products of bacterial growth and disintegration in an overwhelming fashion.

From the foregoing, it appears that in septic obstetrical shock of the kind under consideration, effective treatment should be directed toward rapid and complete removal of the source of infection and toxicity by surgical means. There is ample evidence that such surgical intervention, if it is to be effective, should be carried out within 12 hours or less of the onset of hypotension. If delayed beyond this period, it may not influence the downward course of the patient's illness

In most cases, instrumental evacuation of the uterus *per vaginam* is the indicated procedure, unless there is doubt that this can be done effectively and completely without major operative trauma. Under these circumstances, resort to a rapid hysterectomy may be both preferable and justifiable. On the other hand, when the fetus and placenta have been passed, or removed manually or by instruments and with confidence that the evacuation has been a complete one, and the condition of the patient remains grave, hysterectomy does not appear rational[31].

As was stated in the opening paragraph of this review, it is of some interest that the occurrence of even a small number of cases of acute and fatal toxic puerperal septicemia can have been noted in so brief and recent a period of time. A further point of interest is the fact that a majority of the cases were seen in only two institutions[4,31]. The latter circumstance is doubtless a fortuitous one reflecting, in part at least, the fact that both hospitals are located in metropolitan centers and receive a considerable number of indigent or ill-fortuned women who have attempted to abort themselves by local manipulations. Despite this, an obstetrical implication of wider significance is affirmed by the fatal outcome in the several patients in whom abortion or labor occurred spontaneously. Like the patients in whom self-manipulation was acknowledged, most of these women were in the second trimester of pregnancy when abortion threatened, and the initial symptom was usually a leakage of amniotic fluid. The latter accident is not currently regarded as posing significant septic hazards for the expectant mother at any maturity of pregnancy, so long as the inevitable abortion or labor which ensues is not a protracted one, and ordinary hygienic precautions are observed. Once labor or abortion begins, however, it is generally recognized that the danger of genital infection rises with any undue delay in the evacuation of the uterus. The appearance of fever bodes ill for both fetus and mother, and from what has been recorded here, it would appear to merit special vigilance if it is observed in any desultory labor or abortion occurring in the middle months of pregnancy.

REFERENCES

(1) **Altemeier, W. A.,** and **Cole, W.:** Ann. Surg., **143,** 600, 1956.
(2) **Bennet, I. L.,** and **Beeson, P. W.:** Medicine, **29,** 365, 1950. (3) **Borden, C. W.,** and **Hall, W. H.:** New England J. Med., **245,** 760, 1951. (4) **Bradford, W., Hoffman, G.,** and **Bachman, C.:** To be published. (5) **Braude, A. I., Williams, D., Siemienski, J.,** and **Murphy, R.:** A.M.A. Arch. Int. Med., **92,** 75, 1953. (6) **Burrows, W.:** Ann. Rev. Microbiol., **5,** 181, 1951.
(7) **Delaunay, A., Boquet, P., Lebrun, J., Leboult, Y,** and **Delaunay, M.:** J. physiol. (Paris), **40,** 89, 1948. (8) **Douglas, R. G., Buchman, M. I.,** and **MacDonald, F. A.:** J. Obst. & Gynec. of the Brit. Emp., **62,** 727, 1955. (9) **Doumulin, J. G.,** and **Steed, G. R.:** Ibid., **63,** 739, 1956.
(10) **Ebert, R. V.,** and **Stead, E. A., Jr.:** J. Clin. Invest., **20,** 671, 1941. (11) **Essex, H. E.,** and **Thomas, W. D.:** Proc. Staff Meet., Mayo Clinic, **25,** 34, 1950.
(12) **Freedberg, A. S.,** and **Altschule, M. D.:** New England J. Med., **233,** 560, 1945.
(13) **Hall, W. H.,** and **Gold, D.:** A.M.A. Arch. Int. Med., **96,** 403, 1955. (14) **Hinshaw, L. B.,** and **Bradley, G. M.:** Am. J. Physiol., **189,** 329, 1957.
(15) **Janeway, T. C.:** New York Med. J., **85,** 193, 1907.
(16) **Lane, F. E.:** Discussion of **Douglas *et al.*[8].** (17) **Liedberg, N. C-F., Reiss, E.,** and **Artz, C. P.:** Surg., Gynec. & Obst., **99,** 151, 1954.

(18) **MacLean, L. D.,** and **Weil, M. H.:** Circulation Res., **4,** 546, 1956. (19) **Martin, W. J.,** and **Nichols, D. R.:** Proc. Staff Meet., Mayo Clinic, **31,** 333, 1956. (20) **Nauts, H. C., Swift, W. E.,** and **Coley, B. L.:** Cancer Res., **6,** 205, 1946. (21) **Penner, A.,** and **Klein, S. H.:** J. Exper. Med., **96,** 59, 1952. (22) **Pennisi, J. A., Lawrence, G. J., Jr.,** and **Veprovsky, E. C.:** Am. J. Obst. & Gynec., **76,** 1294, 1958. (23) **Reid, D. E.:** Ibid., **73,** 697, 1957. (24) **Reilly, J., Rivalier, E., Compagnon, A., Laplane, R.,** and **du Buit, H.:** Ann. med. (Paris), **37,** 21, 1935. (25) **Romberg, E., Pässler, H., Bruhus, C.,** and **Müller, W.:** Deutsch. Arch. klin. Med., **64,** 652, 1899. (26) **Schwartzman, G.:** The Phenomenon of Local Tissue Reactivity. New York: Paul B. Hoeber, Inc., 1937. (27) **Spink, W. W.:** J. Am. Med. Assn., **152,** 585, 1953. (28) **Spittel, J. A., Martin, W. J.,** and **Nichols, D. R.:** Ann. Int. Med., **44,** 302, 1956. (29) **Stead, E. A., Jr.,** and **Ebert, E. V.:** Med. Clin. N. America, **24,** 1387, 1940. (30) **Stough, W. V.,** and **Skinner, J. J.:** Am. J. Obst. & Gynec., **72,** 1349, 1956. (31) **Studdiford, W. E.,** and **Douglas, G. W.:** Ibid., **71,** 842, 1956. (32) **Tenney, B., Little, A. B.,** and **Wamsteker, E.:** New England J. Med., **257,** 1022, 1957. (33) **Thomas, L.:** Ann. Rev. Physiol., **16,** 467, 1954. (34) Idem: A.M.A. Arch. Int. Med., **101,** 452, 1958. (35) **Thomas, W. D.,** and **Essex, H. E.:** Am. J. Physiol., **158,** 303, 1949. (36) **Van Slyke, D. D.:** Ann. Int. Med., **41,** 709, 1954. (37) **Waisbren, B. A.:** A.M.A. Arch. Int. Med., **88,** 467, 1951. (38) **Warren, H. D., Balboni, V. G., Rogliano, F. T.,** and **Feder, A.:** New England J. Med., **232,** 671, 1945. (39) **Weil, M. H., MacLean, M. D., Spink, W. W.,** and **Visscher, M. B.:** J. Lab. & Clin. Med., **48,** 661, 1956. (40) Idem: J. Clin. Invest., **35,** 1191, 1956. (41) **Weil, M. H.,** and **Spink, W. W.:** J. Lab. & Clin. Med., **50,** 501, 1957. (42) Idem: A.M.A. Arch. Int. Med., **101,** 184, 1958. (43) **Wise, R. S., Shaffer, J. M.,** and **Spink, W. W.:** J. Lab. & Clin. Med., **40,** 961, 1952. (44) **Zahl, P. A.,** and **Hunter, S. H.:** Tr. New York Acad. Sci., **14,** 161, 1952.

PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF MARCH 17, 1959

Observations on the Reabsorption of Water and Certain Electrolytes by the Proximal Tubules of the Kidneys of Rats.* PHYLLIS A. BOTT, PH.D., AND JUDITH B. LITCHFIELD, PH.D. (Department of Physiological Chemistry, Woman's Medical College). In two types of experiments ("Normal"—during infusion of 10% inulin in .9% NaCl at a rate of about 1.6 ml. per hour and "Forced diuresis"—during infusion of 20% mannitol at .18 ml./min.) tubule fluid, serum and ureteral urine were collected, using the general techniques as described in papers from the laboratory of A. N. Richards. Sites of puncture were determined by the neoprene cast method of Bott. In normal experiments the urine flow was usually between .1 and .5 ml. per hr. per kidney (pH 4.8 to 5.9). Proximal tubule fluid to serum ratios varied from 1.6 to 3.95 for inulin, .89 to .96 for potassium, 1.08 to 1.20 for sodium and 1.25 to 1.40 for chloride (serum values corrected for water and Donnan). The chloride ratios confirm those of Walker, Bott, Oliver and MacDowell. One pH determined at 50% proximal was 7.0. In mannitol diuresis (no inulin determined) urine flows are usually from 8 to 12 ml. per hr. per kidney (pH approximately 7). Rates of collection of proximal tubule fluid were approximately five times as great as in "Normal" experiments. Fluid to serum ratios were .92 to .99 for potassium, 1.02 to 1.05 for sodium and .97 to 1.02 for chloride. Results suggest that water and sodium reabsorption are greatly reduced in the proximal tubule and also support the probability of an osmotic ceiling in proximal tubule fluid. Rates of collection of a few distal tubule fluids during diuresis were like those from the proximal tubule. Potassium concentrations drop and sodium and chloride drop markedly. Sodium and chloride outputs in the mannitol experiments are greater than in the "Normal" experiments but still are only a small fraction of the amounts filtered.

The Mecholyl and Cold Pressor Tests as Indicators of Autonomic Reactivity in Mental States. By KARL RICKELS, M.D., AND JAMES H. EWING, M.D., (Department of Psychiatry, University of Pennsylvania). The concept of autonomic activity-reactivity seems to be fruitful for studying mental illness. The Mecholyl test, which measures cardiovascular response to an injection of 10 mg. Mecholyl subcutaneously, has been used in psychiatric research as an index of sympathetic reactivity. Because of contradictory reports in the literature, a reliability study was undertaken for this test. Another procedure presumably measuring sympathetic nervous system reactivity is the cold pressor test which has not been extensively used in psychiatric research. Therefore a reliability study for this test was also made and correlations were sought between Mecholyl and cold pressor tests. A series of Mecholyl test-retests was performed in 37 psychotic in-patients and

*Supported by grant from the Life Insurance Medical Research Fund.

systolic blood pressure group, area, maximum drop, maximum increase, homeostasis and compensatory overshoot were used as indices for correlation. Cold pressor test-retest correlations were also run for 17 patients and 14 normals. Spearman rank order correlations were applied to all test-retest series. Our findings may be summarized as follows: 1) Good test-retest reliability was found for the Mecholyl test in psychotic subjects and for the cold pressor tests in normal and psychotic subjects. The best correlations were found with various indices derived from systolic blood pressure data. 2) There is a significant inverse relationship between the blood pressure responses to Mecholyl and cold pressor stress. Furthermore, patients with a short hypotensive Mecholyl curve followed by marked compensatory rise above baseline level gave significantly higher cold pressor responses than patients with a normoreactive Mecholyl curve. 3) The cold pressor response is enhanced by a prior injection of Mecholyl in patients with high sympathetic reactivity but not in patients with a normal or low sympathetic reactivity. 4) These results suggest confirmation of Gellhorn's theory of the enhancement of sympathetic response in subjects with high sympathetic reactivity by the injection of Mecholyl.

A Critical Evaluation of Isotopic Methods in the Determination of Cardiac Output. BARBARA L. CARTER*, M.D., SIGURD E. JOHNSEN†, M.D., R. KENNETH LOEFFLER, M.D., AND MARTHA SOUTHARD, M.D. (Departments of Radiology and Physiology, Temple University School of Medicine). An accurate determination of the cardiac output can be made with radioactive isotopes using peripheral arterial blood. This blood is passed through plastic tubing coiled in a deep well scintillation counter. The inscribed curve representing counts per minute is then calibrated by passing a laboratory standard through this same tubing.

$$\text{Cardiac output} = \frac{\text{Total Dose}}{\text{Area under curve}}$$

External body surface counting is now being widely used as a routine clinical procedure for the measurement of cardiac output. A scintillation counter over the anterior chest wall measures the number of counts per second as the isotope passes through the heart. This curve is calibrated in terms of μc. per ml. by counting over the same area (10 minutes later) after the isotope has become well distributed throughout the blood volume. A simultaneous venous sample is withdrawn to determine the μc. per ml.

$$\text{Cardiac output} = \frac{\text{Total Dose} \times \text{final counts per second}}{\text{Area under curve} \times \text{conc.venous blood}}$$

This precordial method yields results 1 or 2 times the true output. Experiments have shown that this apparent output will vary with the size of the collimator used, with any change in the relative position of the detector over the heart, and with varying distances between the detector and the heart. Significant errors are introduced with slight changes in the position of the patient during the procedure, with a zero drift of the instrumentation and with differences in interpretation of the downstroke of the curve. The precordial determination cannot be accurately calibrated, since this does not permit the isolation of a known volume

*National Institute of Health Trainee, Post-doctoral #635, 1956–1957.
National Institute of Health Fellow, Research Grant #Hf8287, 1958.
†National Institute of Health Trainee, Post-doctoral #603, 1956–1957.

of arterial blood. If the detector is placed over the aorta, the vena cava will not contain any isotope during the recording of the initial curve but will contain some isotope later when the final counting rate is being recorded for the calibration of the initial curve. This will increase the effective volume of blood containing isotope and will invalidate the calibration. The precordial technique is, therefore, unsound for a routine clinical procedure.

Effect of Changes in Pulmonary Blood Pressure and Flow on the Lung's Capillary Bed, Using the Diffusing Capacity for CO as an Index of Its Size. E. E. ROSENBERG, PH.D., AND R. E. FORSTER, M.D. (Department of Physiology and Pharmacology, Graduate School of Medicine, University of Pennsylvania). The relative importance of variations in blood pressure and flow on the size of the pulmonary capillary bed was investigated, the pulmonary capillary bed being defined as consisting of all blood vessels through whose walls gas exchange takes place. The diffusing capacity of the lungs for carbon monoxide (D_L) is considered an index of the size of the total pulmonary capillary bed, increases in D_L are taken as indications that the size of the bed has increased and decreases in D_L to mean decreases in it.

Isolated cat lungs were perfused with the animal's own blood at 37° C., via cannulae in the pulmonary artery and left atrium, and ventilated by negative pressure. D_L was measured at constant volume by a modification of the single breath technique (*J. Clin. Invest.*, **33**, 1135, 1954). Pulmonary blood flow was varied by altering the rate of the blood pump; intravascular pressures, as referred to atmospheric, were varied by changing the outflow pressure.

In 3 lungs in which the pulmonary blood flow was increased from 50 to 225 ml. per min. while outflow pressure was held constant, D_L increased on the average by 50%. Mean intravascular pressure, taken as the average of pulmonary arterial and left atrial pressure, increased with the blood flow in these experiments. Raising mean intravascular pressure in 4 lungs by increasing outflow pressure at constant blood flow increased D_L on the average by about 30% per 10 mm. increase in pressure. In 4 experiments in which outflow pressure was *lowered* while blood flow was *increased* there was no demonstrable increase in D_L.

We conclude that the pressure across the walls of the pulmonary blood vessels is a primary factor in controlling the size of the pulmonary capillary bed as measured by D_L. No independent effect of flow was observed.

BOOK REVIEWS AND NOTICES

REMBRANDT'S ANATOMY OF DR. NICOLAAS TULP. AN ICONOLOGICAL STUDY. BY WILLIAM S. HECKSCHER. Pp. 278; 70 ills., 1 color plate. New York: New York University Press, 1958. Price, $15.00.

THIS book surveys the art of painting in the early 17th century and especially of Rembrandt's technique in the Tulp portrait. It also presents a critique of Dr. Tulp's medical activities. It was a recent cleaning of the "Anatomy," bringing out unexpected new features, that gave the stimulus to Mr. Heckscher for a new intensive study of this, Rembrandt's first great painting.

Physicians will be most interested in the study of Dr. Tulp's "Anatomy" itself. We see the celebrated Dr. Tulp the only one wearing a hat and the only one seated (the old *magister cathedraticus*), demonstrating a dissection of the arm of an executed criminal. Behind him stand members of the Guild of Surgeon-Anatomists peering eagerly at the dissection. Such public "Anatomies" had been an annual entertainment in several countries from the 15th to the 18th centuries; in Amsterdam they were open to all classes, and, coming only once a year at the height of the winter season, ranked first among the public entertainments in that city. Dr. Tulp's "Anatomy," given in January, 1632, shows him lecturing on the tendons of the forearm which he holds in his forceps (suggesting action to the author). Rembrandt's anatomical blunder, to which the author refers apparently consisted in painting the flexors as attached to the lateral epicondyle (radial) of the humerus instead of to the medial (ulnar) epicondyle. The obviously longer left arm is another example of Rembrandt's occasional lack of care in portraying human anatomy. A change found after the re-cleaning is seen in the paper held by one of the onlookers: a page of an anatomical atlas now shows a list of the guild members. In Plate 48–57 traces of an arm are clearly visible beneath the names.

The artistic side, the largest portion of this comprehensive study, must be treated only in a few words. The artistic conventions that influenced the young Rembrandt without limiting his originality; the origin of Tulp's name—he always signed himself Claes Pieterszoon (Nicolaus Petrous)—and his career; Rembrandt's warm appreciation of Dr. Tulp and *vice-versa;* these are a few samples of matters treated in detail in morsels scattered through the book. Naturally one finds defects such as occasional far-fetched deductions and unlikely allocations. A conspicuous error appears in the reference to Hogarth's "fourth stage of cruelty," (see Fig. 19) where the subject is said to be "writhing" on the table in living torture as punishment; yet clearly the necropsy is at a stage that could not possibly have been reached in a living subject. It is difficult to agree with the author's concept of an "Anatomy" as in part sacrificial, in part ritual, and in part a scene of justice. Frequent phrases, such as "very probably," "must have been," "tempting to assume," "hazard a guess," often hinder acceptance of conclusions reached. Nor does an occasional word such as "exogenesis," insufficiently explained, help toward easy reading. The arrangement of notes, bibliography and index, separated first by appendices, then by the plates, is inconvenient and annoying, especially as much information is contained in the 233 notes (56 pages) and 532 items (24 pages) of the Bibliography. The 8 pages of the Index in the copy being reviewed are in duplicate and stop at "Offuys," we hope that this error is not repeated in other copies. The illustrations, 21 distributed through the text, and the 48 full page plates (many with several to a plate) are excellent, especially the plates. They show clearly what they are supposed to show, and have adequate legends which regularly indicate source and provenance.

To summarize the pros and cons, this book can be with confidence assessed as a prodigious and monumental achievement.

E.K.

SUBCELLULAR PARTICLES IN THE NEOPLASTIC PROCESS. BY CORNELIUS P. RHOADS, HILARY KOPROWSKI AND 37 OTHERS. Ann. New York Acad. Sci., 68, Art. 2, pp. 245–656, 1957. New York: New York Academy of Sciences, 1957. Price, $5.00.

THIS is a monograph of a symposium concerned with the relation of subcellular particles to carcinogenesis held by the New York Academy of Sciences in October, 1957. As Andervont states in a general summary of the Conference, for an adequate survey of the material presented one would require a competent virologist, bacteriologist, patholo-

gist, immunologist and geneticist. Three tumors in which the involvement of viruses is clear are considered. The first and earliest tumor virus studied is that of fowl leukosis. The disease is contagious, and yet many chickens exposed to it do not develop the disease. Studies in this connection point out that a pure clone of virus can become contaminated by genetic variation or mutations. Observations also indicate that tumor viruses may likewise be altered by transduction and transformation.

The second virus tumor discussed is the Rous chicken sarcoma discovered in 1911. Unlike the fowl leukosis virus which can be considered to be a complex, the Rous sarcoma virus initiates a definite tumor at its site of inoculation, and it displays excessive activity. Considerable studies have been accomplished in the purification of the virus. Nevertheless, the great difficulty lies in the inability to recover the virus in the tumor it induces.

A section of the monograph deals with the difference between chemically-induced and virus-induced tumors. The interest in this question is due to the obvious fact that there may be various methods of inducing tumors without the agency of viruses; but, as Andervont points out, none of the contributors have claimed that all tumors are referable to viruses.

The third virus induced-tumor is the mammary cancer in mice, discovered in 1936. It is transmitted by the mother's milk (Bittner agent), and some of its biological properties are known. Since the disease occurs only in some strains of mice, genetic significance is thus emphasized as well as hormonal factors. In other words, genetic susceptibility and proper hormonal stimulation appear to be the requisite to demonstrate this important agent in breast cancer of mice. In brief, a balance of three factors are required for the development of breast cancer: the milk agent, genetic constitution and hormonal stimulation. Nevertheless, under appropriate conditions the virus is unnecessary to develop breast cancer in mice. Forced breeding, carcinogenesis, synthetic estrogens, or transplanted pituitaries can lead to the production of breast cancer in mice. It is thus emphasized that the virus is not implicated in all mammary cancer of mice, so that the etiology may be wholly different and nonviral in other types of breast cancer. Furthermore, as mentioned, even the mammary cancer virus is dependent on genetic and hormonal factors in order to elicit tumors. It is also important to point out that whereas the Rous virus rapidly induces a neoplasm, the mammary tumor virus can remain dormant in the host for many years, and even be unable to cause the formation of neoplasia.

The studies of L. Gross on the transmission of the leukemia virus in newborn mice raises interesting new problems. Considerable studies will be required, as pointed out by one investigator, in evaluating the necessity of newborn mice as test animals for the presence of the leukemia virus. Complications arise from the fact that inoculated newborn mice develop besides leukemia, also parotid tumors and subcutaneous sarcomas, suggesting that the virus produces a "complex" that needs further unravelling.

The monograph is comprehensive and full of abundant and important material to workers in cancer research. V.M.

MAKROGLOBULINÄMIE WALDENSTRÖM. Edited By G. RIVA. Authors: A. HÄSSIG, Bern; F. HEINZLER, Düsseldorf; H. ISLIKER, Bern; K. JAHNKE, Düsseldorf; R. KAPPELER, Bern; A. KREBS, Bern; J. J. SCHEIDEGGER, Gent; W. SCHOLTAN, Wuppertal; R. WEBER, Bern, und H. U. ZOLLINGER, St. Gallen. Volume 25 (1958). Pp. 183. Basel and Stuttgart: Benno Schwabe & Co., 1958 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $4.25.

This monograph consists of reprints of five papers published in 1958 in Helvetica Medica Acta. It is introduced by the outstanding European hematologist Rohr with a discussion of the relationship between myeloma, lymphatic leukemia and certain reticuloses. These proliferative diseases all originate in the reticulohistiocytic system (RHS) (Rohr's nomenclature), that is, the undifferentiated mesenchyme (in our nomenclature). In the first paper of this series Jahnke and associates compare the viscosity of various gammaglobulins including cryoglobulins and macroglobulins. The viscosity of sera increases with the concentration of proteins and their increasing deviation from the globular shape. The highest viscosity is seen in sera containing macroglobulins whose long axis is 8.1 to 9.5 times that of the short axis. In the second paper Scheidegger and associates report their ring precipitation and immunoelectrophoretic studies in macroglobulinemia. Each patient has his own immunologically specific macroglobulins, which also contain the beta-two-macroglobulin determinant of normal beta-two-macroglobulins. In the third paper Isliker observes that the

macroglobulins differ from normal gammaglobulin in that they contain 2 to 3 times as much carbohydrate and 6 to 10 times as much sialic acid. Special attention is drawn to a reversible association-dissociation phenomenon caused by addition or removal of sulfhydryl compounds. In the fourth rather lengthy paper Kappeler and associates compare the clinical picture of 21 new cases with that of 126 cases from the literature. A malignant form leading to death in a short time is distinguished from a relatively benign form lasting for many years. The macroglobulinemia resembles myeloma in that it is due to a neoplastic growth of lymphoid and plasma cells, a lymphoid-plasma cellular reticulomatosis, which can be diagnosed irreproachably only by histological examination of bone marrow, lymph nodes or other tissues. In the last paper Zollinger describes the pathological anatomy of macroglobulinemia. This is characterized by focal or diffuse infiltrations of "reticular lymphoid cells" and plasmocytes, both typical and atypical. The bone marrow is involved in all cases, the lymph nodes in many cases. The distribution of the infiltrates resembles that of leukemia. The disease differs from plasmocytoma by generalized involvement of the medullo-lympho-hepatic system. Each paper is concluded by a summary in German, French and English. The book is highly recommended to all students of hyperglobulinemia.

W.E.

OBSTETRICAL PRACTICE. By ALFRED C. BECK, M.D., Professor Emeritus of Obstetrics and Gynecology, and ALEXANDER H. ROSENTHAL, M.D., Clinical Associate Professor of Obstetrics and Gynecology, State University of New York College of Medicine at New York City. 7th ed. Pp. 1115; 955 ills. Baltimore: The Williams & Wilkins Co., 1958. Price, $14.00.

THE preparation of a textbook of obstetrics which will serve both as a student text and as a reference for physicians in practice presents a difficult problem. Beck's Obstetrical Practice, now under the combined authorship of Beck and Rosenthal serves this purpose admirably and the fact that the current edition is the seventh attests to its value. This book has always been an excellent student text because basic physiologic mechanisms, diagnostic principles and methods of management have been stressed and clearly and completely presented. It also has included enough material concerning abnormalities and obstetric operative procedures to make it a valuable addition to the library of the practicing physician. The inclusion of much new information and the deletion of outdated material makes this edition even more worthwhile than those which preceded it.

The chapters on placental structure and function and on trophoblastic abnormalities have been rewritten. Because there is a considerable difference of opinion concerning some of the material in this area the views of several authorities are presented. All the chapters concerning normal and abnormal labor have been revised to include current concepts, but fortunately the authors have not discarded their own sound practices simply because others are currently more fashionable.

The illustrations are for the most part simple line drawings done by the senior author, but appropriate ones have been borrowed, mostly from original papers rather than from other textbooks. They are plentiful, clear and well placed with regard to the text. The Bibliography is inclusive and new studies as well as classic background references are included. The style is clear, simple, interesting and easy to read.

This book will continue to be one of the best obstetric texts available in this country and might well be in the library of general and specialized practitioners as well as of medical students.

J.W.

HANDBUCH DER TUBERCULOSE, BAND I, ALLGEMEINE GRUNDLAGEN. Edited by J. HEIN, Tonsheide, H. KLEINSCHMIDT, Honef, E. UEHLINGER, Zurich. Pp. 832; 244 ills. Stuttgart: Georg Thieme Verlag, 1958 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, DM 178 ($42.40).

THIS first volume of five carries on the tradition of the great Handbuchen on tuberculosis published in prewar Germany. The history of tuberculosis is not only covered in the first chapter by Loeffler of Zurich but also reviewed in its special applications throughout the book. The excellent chapters by Suter and Bloch on bacteriology and immunity link work in this country with European studies. Complete bibliographies of almost all of the subjects covered in other chapters also show the preponderance of American and German work. Allergy, in all of its manifestations relative to tuberculosis including the basis of the tuberculin test, is most thoroughly discussed. Diehl's chapter on native resistance is unequalled elsewhere in medical literature. Epidemiologic and environmental aspects of

tuberculosis are fully covered and illustrated by numerous and invaluable graphs.

To indicate the broad approach of the whole book Suter may be quoted: "Tuberculosis is not merely an infectious disease which must be fought against, but also a biologic problem which demands a solution." As a reference work and for all those studying the fundamentals of tuberculosis, allergy, immunity and native resistance to infection this handbuch is highly recommended.

J.W.

CARDIAC ARREST AND RESUSCITATION. Edited by HUGH E. STEPHENSON, JR., M.D., Professor and Chairman, Department of Surgery, University of Missouri. Pp. 378; 30 ills. St. Louis: The C. V. Mosby Co., 1958. Price, $12.00.

THE author of this book is well-known, particularly for his efforts in establishing The Cardiac Arrest Registry at the University of Missouri School of Medicine where he is Professor and Chairman of The Department of Surgery. Study of more than 1700 collected and personal cases has allowed for the formulation and organization of knowledge regarding the nature, recognition and treatment of cardiac arrest and is the basis of this book. Its chapters are concerned with history, incidence, diagnosis and etiology. Also, there are chapters on treatment, prophylactic and active, and prognosis, immediate and long-term. Even the medicolegal aspects are included. Finally, an informative discussion on the use of elective cardiac arrest in open-heart surgery is given by Dr. Kolff. It is, indeed, a nosology of cardiac arrest. From the extent of the bibliography, the author has apparently surveyed everything ever written about the subject and has intertwined this knowledge with his own experience. Sudden cardiac arrest is increasing in incidence and has become one of the chief hazards of modern anesthesia and surgery. We have hardly tapped the surface in medical illnesses. Cardiac arrest is a 3-minute emergency. The nearest doctor, regardless of interest, is expected to act without delay, so the time to learn about cardiac arrest is now.

J.Z.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

Published Monthly. Illustrated.

Subscription price: 1 year $10.00; 2 years $18.00.

(One year subscription to Canada, South and Central America, Philippines and Spain, $10.50; all other countries $12.00)

All foreign subscriptions payable in advance in United States dollars.

Business Correspondence: Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, Pa.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence should be sent to the Editor:

DR. RICHARD A. KERN, Temple University School of Medicine, Philadelphia 40, Pa.

Articles are accepted for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side only, of good quality paper and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle.

ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. Line drawings and charts should be prepared with black India ink. Special arrangements can be made for printing color plates, elaborate tables or an excessive number of illustrations.

REFERENCES should be numbered and at the end of the articles arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

100 REPRINTS will be supplied gratis. Covers will be omitted on all articles. Orders of additional reprints will be supplied in multiples of 100. An order form showing cost of reprints is sent with proof. Individual reprints can usually be obtained by writing directly to the author.

Index photographed at t
beginning for the conve
of the microfilm user.

aphed at the
the convenience
lm user.

Copy

Index Number

Vol. 237, No. 6 JUNE, 1959 No. 1946

PROPERTY OF
THE DEPARTMENT OF PATHOLOGY
THE UNIVERSITY OF MICHIGAN

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

REG. U. S. PAT. OFF.
ESTABLISHED 1820

AUG 15 1960

MEDICAL LIBRARY

Editor
RICHARD A. KERN, M.D.

Associate Editor
THOMAS M. DURANT, M.D.

Assistant Editor
CHRIS J. D. ZARAFONETIS, M.D.

Carl Bachman, Herman Beerman, Wm. L. Benedict, A. M. Bongiovanni, George E. Burch, McKeen Cattell, Franklin G. Ebaugh, Noah D. Fabricant, James Galvin, Harry Gold, John E. Gordon, David M. Gould, Theodore H. Ingalls, N. R. Ingraham, Jr., C. G. Johnston, William D. Love, John G. McAfee, Gardner C. McMillan, A. Harry Neffson, Franklin L. Payne, I. S. Ravdin, Roger W. Reed, H. P. Wagener, Irving J. Wolman

The Epidemiological Approach to Human Ecology. By THOMAS FRANCIS, JR., M.D. 677

Comparison of the Granuloma Producing Capacity of Normals and Sarcoid Granuloma Patients: Experimental Analysis of the Sarcoid Diathesis Theory. By HARRY J. HURLEY, M.D., D.Sc.(MED.) and WALTER B. SHELLEY, M.D., PH.D. 685

Effect of Food on the Absorption of Erythromycin Propionate, Erythromycin Stearate and Triacetyloleandomycin. By HANS A. HIRSCH, M.D. and MAXWELL FINLAND, M.D. 693

Effects of Certain Pure Long Chain Polyunsaturated Fatty Acid Esters on the Blood Lipids of Man. By HOWARD E. WORNE, PH.D., D.Sc. and LAWRENCE W. SMITH, M.D. 710

Renal Function in Liver Disease and Malnutrition. By IVAN DUQUE, M.D., IVAN JIMENEZ, M.D. and GUILLERMO LATORRE, M.D. 722

Ascites: Etiologic Considerations with Emphasis on the Value of Several Laboratory Findings in Diagnosis. By MORTON E. TAVEL, M.D. 727

The Pansystolic Regurgitant Murmur: A Simple Method of Identifying Its Anatomic Source. By LOUIS A. SOLOFF, M.D., FELIX CORTES, M.D., WILLIAM L. WINTERS, JR., M.D. and JACOB ZAT CHNI, M.D. 744

The Treatment of Mumps Orchitis with Prednisone. By EDWARD S. MONGAN, CAPT. MC. 749

Correlation of Smoking Habits with Hemolytic Streptococci and Antistreptolysin O Responses. By MILTON S. SASLAW, M.D. and MURRAY M. STREITFELD, PH.D. 754

An Electrically Balanced Bipolar Vectorcardiographic System: Lead Analysis and Lead Synthesis Using the dR Factor. By LAWRENCE E. LAMB, M.D. and GEORGE B. SMITH, JR., MAJOR, USAF (MC)FS 759

Lactic Dehydrogenase Versus Glutamic Oxalacetic Acid Transaminase as a Diagnostic Test for Myocardial Infarction. By IRVING FREEMAN, M.D., DEBORAH A. JACKSON, B.S. and CHARLES S. COLLIER. 768

Inhibition of Lipid Mobilization of Surgical Stress by Partially Depolymerized Hyaluronic Acid. By CHRIS J. D. ZARAFONETIS, M.D., JOSEPH SEIFTER, M.D., DAVID BAEDER, PH.D., JOHN P. KALAS, M.D. and WALTER Y.M. CHANG, M.D. 771

Progress of Medical Science

Pediatrics—**Neonatal Hematopoiesis: A Commentary.** By ROBERT D. GENS, M.D. 781

Gynecology and Obstetrics—**Bacteremic Shock in Obstetrics.** By W. Z. BRADFORD, JR., M.D. and CARL BACHMAN, M.D. 785

Physiology—**Proceedings of The Physiological Society of Philadelphia** 791

Book Reviews and Notices 794

OWNERS AND PUBLISHERS LEA & FEBIGER PHILADELPHIA 6, PENNA.

Copyright, 1959, by Lea & Febiger. All Rights Reserved. Second Class Postage Paid at Philadelphia, Pa.

PUBLISHED MONTHLY, SUBSCRIPTIONS, $10 a Year, $18 for 2 Years

NOW... "CHEMICAL PACKAGING" THROUGH CHELATION* CREATES A CLINICALLY SUPERIOR ORAL IRON

chelate "packaging" protects against iron loss or irritation in transit through g.i. tract **...may be given with meals or ulcer medication without loss of therapeutically available iron... or may be taken on an empty stomach without irritation** *—because chelated iron is not ionized and resists precipitation by alkali, protein, phosphate, or phytate.*

chelate "packaging" ensures physiologic acceptance of iron on delivery to intestinal mucosa... **proved clinically effective in moderate or severe hypochromic anemia[1] yet minimizes risk of toxicity on accidental overdosage** *—because chelation keeps iron in solution over an extended mucosal area for rapid uptake as required, yet inhibits excessive diffusion of iron into the circulation.*

CHELATED IRON

clinically superior in toleration, safety, and physiologic uptake

FERROLIP®

(Iron Choline Citrate†)

TABLETS

SYRUP

PEDIATRIC DROPS

Supplied: FERROLIP TABLETS, SYRUP, and PEDIATRIC DROPS. Daily adult dose of 3 tablets or 1 fl.oz. syrup provides equivalent of 120 mg. elemental iron. Bottles of 100 and 1000 tablets; syrup in pints and gallons. Each cc. of pediatric drops provides 25 mg. elemental iron. In 30-cc. unbreakable plastic squeeze bottles.

Also available: During pregnancy—FERROLIP ob Tablets, chelated iron with vitamin-mineral essentials; phosphorus-free. **For macrocytic and microcytic anemias-FERROLIP plus** (Capsules and Liquid), chelated iron plus other recognized hematopoietic factors.

*CHELATION: "a well-recognized chemical process wherein metallic ions are sequestered and bound into claw-like rings within the chelating molecule... Hemoglobin has long been recognized to be a chelate complex of iron..."[1]

1. Franklin, M. et al.: Chelate Iron Therapy, J.A.M.A. 166: 1185, 1958

Flint, EATON & COMPANY
Decatur, Illinois

†U.S. PAT. 2,575,

AN AMES CLINIQUICK™

CLINICAL BRIEFS FOR MODERN PRACTICE

other than glycosuria and ketonuria, what are common urine findings in diabetic coma?

Proteinuria and large numbers of granular casts in the sediment.

Source: Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: The Treatment of Diabetes Mellitus, ed. 9, Philadelphia, Lea & Febiger, 1952, p. 359.

"DIP-AND-READ", COLORIMETRIC TESTS FOR ROUTINE TESTING IN THE OFFICE...AND HOME

ALBUSTIX® BRAND Reagent Strips *for proteinuria.* Bottles of 120.

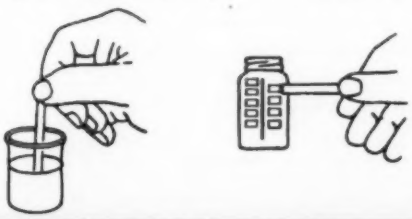
CLINISTIX® BRAND Reagent Strips *for glycosuria.* Bottles of 60.

KETOSTIX® BRAND Reagent Strips *for ketonuria.* Bottles of 90.

URISTIX® BRAND Reagent Strips *for both proteinuria and glycosuria.* Bottles of 125.

PHENISTIX™ Reagent Strips *for phenylketonuria.* Bottles of 50.

AMES
COMPANY, INC.
Elkhart • Indiana
Toronto • Canada



60859

VESPRIN made the difference

SQUIBB TRIFLUPROMAZINE HYDROCHLORIDE

in anxiety and tension states / psychomotor agitation / phobic reactions / obsessive reactions / senile agitation / agitated depression / emotional stress associated with a wide variety of physical conditions

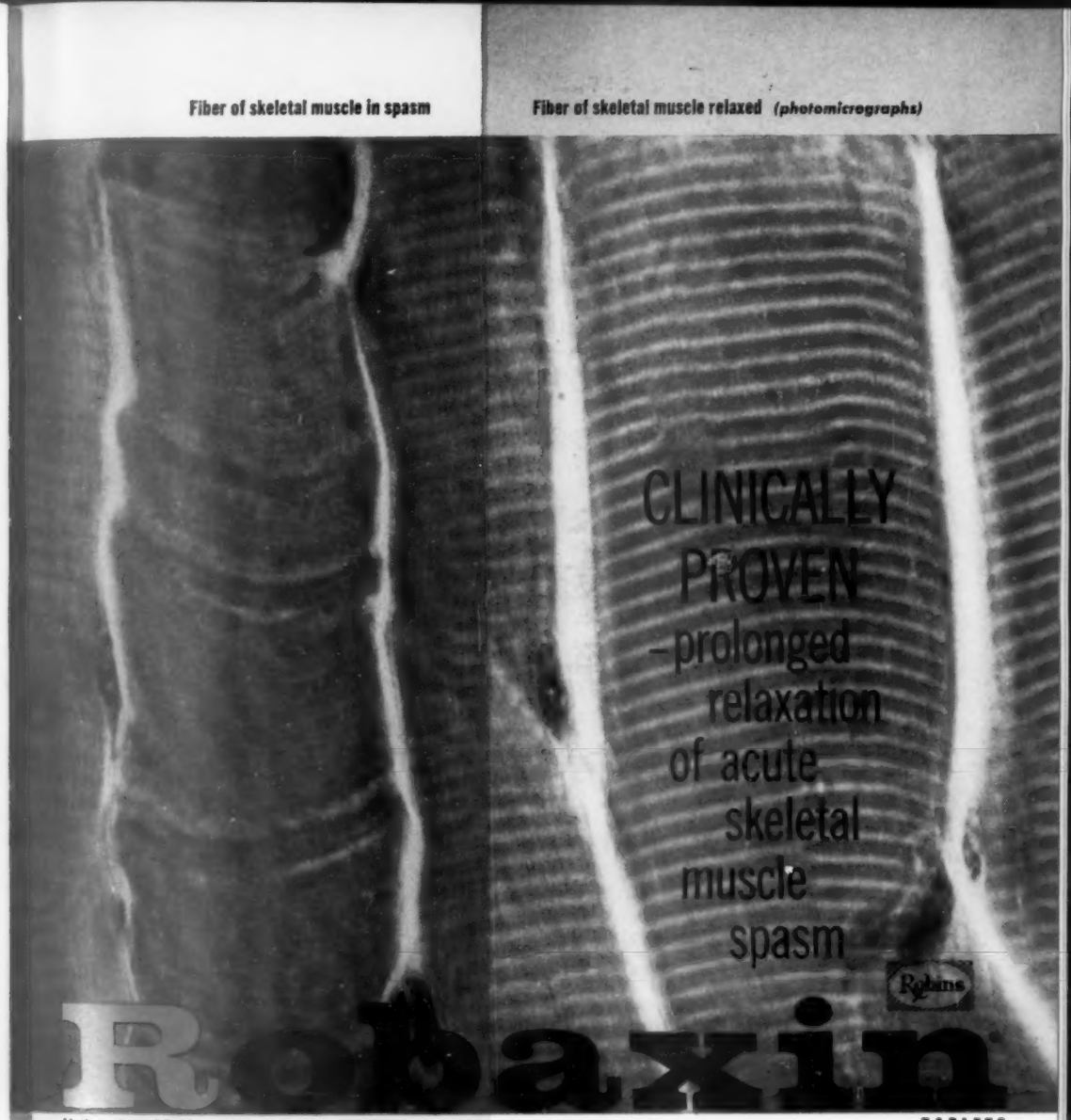
In the patient with anxiety and tension symptoms – Vesprin calms him down without slowing him up... and does not interfere with his working capacity. Vesprin permits tranquilization *without* oversedation, lethargy, apathy or loss of mental clarity.[4]

And Vesprin exhibits an improved therapeutic ratio – enhanced efficacy with a low incidence of side effects; no reported hypotension, extrapyramidal symptoms, blood dyscrasia or jaundice in patients treated for anxiety and tension.[1,2,3]

dosage: for "round-the-clock" control – 10 mg. to 25 mg., b.i.d.; for "once-a-day" use – 25 mg. once a day, appropriately scheduled, for therapy or prevention. **supply:** Oral Tablets, 10, 25 and 50 mg., press-coated, bottles of 50 and 500; Emulsion (Vesprin Base) – 30 cc. dropper bottles and 120 cc. bottles (10 mg./cc.). **references:** 1. Stone, H.H.: Monographs on Therapy *3*:1 (May) 1958. 2. Reeves, J.E. Postgrad. Med. *24*:687 (Dec.) 1958. 3. Burstein, F.: Clinical Research Notes *2*:3, 1959. 4. Kris, E.: Clinical Research Notes *2*:1, 1959. VESPRIN® is a Squibb Trademark.

Vesprin – the tranquilizer that fills a need in every major area of medical practice

SQUIBB
Squibb Quality –
the Priceless Ingredient


Fiber of skeletal muscle in spasm
Fiber of skeletal muscle relaxed (photomicrographs)
CLINICALLY PROVEN
–prolonged relaxation of acute skeletal muscle spasm
Robaxin

Methocarbamol Robins U.S. Pat. No. 2770649 TABLETS

Summary of six published clinical studies:

ROBAXIN BENEFICIAL IN 92.4% OF SKELETAL MUSCLE SPASM CASES

	NO. PATIENTS	RESPONSE			
		"marked"	moderate	slight	none
Carpenter[1]	33	26	6	1	–
Forsyth[2]	58	"pronounced" 37	20	–	1
Lewis[3]	38	"good" 25	6	–	7
O'Doherty & Shields[4]	17	"excellent" 14	2	1	0
Park[5]	30	"significant" 27	–	2	1
Plumb[6]	60	"gratifying" 55	–	–	5
TOTALS	236	184 (73.0%)	34 (14.4%)	4	14

- **Highly potent—and long acting.**[1,2,3]
- **Relatively free of adverse side effects.**[1,2,3,5,6]
- **In ordinary dosage, does not reduce muscle strength or reflex activity.**[1]

REFERENCES: 1. Carpenter, E. B.: Southern M. J. 51:627, 1958. 2. Forsyth, H. F.: J.A.M.A. 167:163, 1958. 3. Lewis, W. B.: California Med. 90:26, 1959. 4. O'Doherty, D. S., and Shields, C. D.: J.A.M.A. 167:160, 1958. 5. Park, H. W.: J.A.M.A. 167:168, 1958. 6. Plumb, C. S.: Journal-Lancet 78:531, 1958.

A. H. ROBINS CO., INC., Richmond 20, Virginia

Ethical Pharmaceuticals of Merit since 1878

IN SHOCK OF

MYOCARDIAL INFARCTION

INJECTION

ARAMINE®

METARAMINOL

provides combined pressor, myocardium-stimulating effect with no tissue slough reported

ARAMINE "Metaraminol combines strong pressor effect with myocardial-stimulating action . . ."[1]

ARAMINE can be administered for balanced pressor, myocardium-stimulating effect by any desired route—intravenous, intramuscular or subcutaneous—with no reported tissue slough and with minimal risk of causing arrythmias. Repeated injections of ARAMINE appear to elicit no tachyphylactic response.

ARAMINE is always ready for immediate use—no dilution is required. These advantages of ARAMINE make it equally valuable in shock accompanying anaphylaxis, brain damage, infectious disease, hemorrhage, surgery, trauma.

Supplied: in 1-cc. ampuls and 10-cc. vials (10 mg. per cc.).

ARAMINE is a trademark of Merck & Co., INC.

ADDITIONAL information is available to physicians on request. Address Professional Service Department, West Point, Pa.

1. Selzer, A. and Rytand, D.A.: COUNCIL ON DRUGS, Report to Council J.A.M.A. 168:762, (Oct. 11) 1958.

MERCK SHARP & DOHME
Division of Merck & Co., INC. Philadelphia 1, Pa.

Butazolidin®

(phenylbutazone GEIGY)

tablets · alka capsules

potent · nonhormonal · anti-inflammatory agent

BUTAZOLIDIN tablets or the Alka capsules are **equally effective but individually adaptable in a wide range of arthritic disorders.**

Recent clinical reports continue to justify the selection of Butazolidin for rapid relief of pain, increased mobility, and early resolution of inflammation.

Gouty Arthritis: "...95 per cent of patients experienced a satisfactory response..."[1]

Rheumatoid Arthritis: In "A total of 215 cases...over half, 50.7 per cent showed at least major improvement, with 21.8 per cent showing minor improvement...."[2] **Osteoarthritis:** 301 cases showed "...a total of 44.5 per cent with complete remission or major improvement. Of the remainder, 28.2 per cent showed minor improvement...."[3] **Spondylitis:** All patients "...experienced initial major improvement that was maintained throughout the period of medication."[3] **Painful Shoulder Syndrome:** Response of 70 patients with various forms showed "...8.6 per cent complete remissions, 47.1 per cent major improvement, 20.0 per cent minor improvement...."[3]

References: 1. Graham, W.: Canad. M. A. J. **79**:634 (Oct. 15) 1958. 2. Robins, H. M.; Lockie, L. M.; Norcross, B.; Latona, S., and Riordan, D. J.: Am. Pract. Digest Treat. **6**:1758, 1957. 3. Kuzell, W. C.; Schaffarzick, R. W.; Naugler, W. E., and Champlin, B. M.: New England J. Med. **256**:388, 1957.

Availability BUTAZOLIDIN® (phenylbutazone GEIGY): Red coated tablets of 100 mg. BUTAZOLIDIN® Alka Capsules containing BUTAZOLIDIN® (phenylbutazone GEIGY), 100 mg.; dried aluminum hydroxide gel, 100 mg.; magnesium trisilicate 150 mg.; homatropine methylbromide, 1.25 mg.

geigy

ARDSLEY, NEW YORK

02555

Quiescence needed

in medical illness in surgery in obstetrics

One of the most versatile agents known, PHENERGAN helps smooth the management of patients under medical, surgical, or obstetrical stress without depressing vital functions. For many areas of general and specialty practice, PHENERGAN has these actions for these benefits:

Sedation: Relieves fear, promotes sleep, encourages cooperation, reduces postoperative excitement—widely useful in obstetrical and surgical sedation.

Antiemesis: Prevents and controls nausea and vomiting associated with motion sickness, surgery, pregnancy, or reflex mechanisms.

Antiallergy: Gives potent and prolonged antihistaminic control of many allergic reactions.

Drug potentiation: Reduces dose requirements of anesthetics, barbiturates, and narcotic analgesics—an important aid to perisurgical and obstetrical management.

PHENERGAN®
HYDROCHLORIDE
Promethazine Hydrochloride, Wyeth
INJECTION • TABLETS • SYRUP • SUPPOSITORIES

Wyeth®
Philadelphia 1, Pa.

Comprehensive literature supplied on request

CONTENTS

ORIGINAL ARTICLES

The Epidemiological Approach to Human Ecology 677
By Thomas Francis, Jr., M.D., Ann Arbor, Michigan.

Comparison of the Granuloma Producing Capacity of Normals and Sarcoid Granuloma Patients: Experimental Analysis of the Sarcoid Diathesis Theory 685
By Harry J. Hurley, M.D., D.Sc.(Med.) and Walter B. Shelley, M.D., Ph.D., Philadelphia, Pennsylvania.

Effect of Food on the Absorption of Erythromycin Propionate, Erythromycin Stearate and Triacetyloleandomycin 693
By Hans A. Hirsch, M.D. and Maxwell Finland, M.D., Boston, Massachusetts.

Effects of Certain Pure Long Chain Polyunsaturated Fatty Acid Esters on the Blood Lipids of Man 710
By Howard E. Worne, Ph.D., D.Sc. and Lawrence W. Smith, M.D., Erlton, New Jersey.

Renal Function in Liver Disease and Malnutrition 722
By Ivan Duque, M.D., Ivan Jimenez, M.D. and Guillermo Latorre, M.D., Medellin, Colombia, S.A.

(Contents continued on page 12)

for the peak of analgesic efficiency

DILAUDID
brand of DIHYDROMORPHINONE

Dosage Forms of Dilaudid hydrochloride:
Ampules: 1cc., 2 mg. and 3 mg. each.
Hypodermic Tablets: 2, 3 and 4 mg. each.
Oral Tablets: 2.7 mg. each.
Multiple Dose Vial: 10 cc., 2 mg. Dilaudid sulfate per cc.

*Subject to Federal narcotic regulations
Dilaudid®, E. Bilhuber, Inc.

KNOLL PHARMACEUTICAL COMPANY ORANGE NEW JERSEY

why ????

WIGRAINE®
FOR MIGRAINE

HERE'S WHY: Wigraine is complete therapy for migraine. Combats all phases of the migraine attack: headache, nausea and vomiting, residual occipital muscle pain. Wigraine is uncoated; disintegrates in seconds, brings fast relief. Wigraine is swallowed easily; no taste or aftertaste problem. In tablets or suppositories, both containing the following time-tested formula:

Ergotamine tartrate	1 mg.
Caffeine	100 mg.
l-Belladonna Alkaloids*	0.1 mg.
Acetophenetidin	130 mg.

*87.5% hyoscyamine and
12.5% atropine as sulfates

for samples write:

Medical Department

Organon Inc., Orange, New Jersey

CONTENTS *(Continued)*

Ascites: Etiologic Considerations with Emphasis on the Value of Several Laboratory Findings in Diagnosis 727
By Morton E. Tavel, M.D., Philadelphia, Pennsylvania.

The Pansystolic Regurgitant Murmur: A Simple Method of Identifying Its Anatomic Source 744
By Louis A. Soloff, M.D., Felix Cortes, M.D., William L. Winters, Jr., M.D. and Jacob Zatuchni, M.D., Philadelphia, Pennsylvania.

The Treatment of Mumps Orchitis with Prednisone 749
By Edward S. Mongan, Capt. MC, El Paso, Texas.

Correlation of Smoking Habits with Hemolytic Streptococci and Antistreptolysin O Responses 754
By Milton S. Saslaw, M.D. and Murray M. Streitfeld, Ph.D., Miami, Florida.

An Electrically Balanced Bipolar Vectorcardiographic System: Lead Analysis and Lead Synthesis Using the dR Factor 759
By Lawrence E. Lamb, M.D. and George B. Smith, Jr., Major, USAF (MC)FS, Randolph Air Force Base, Texas.

Lactic Dehydrogenase Versus Glutamic Oxalacetic Acid Transaminase as a Diagnostic Test for Myocardial Infarction 768
By Irving Freeman, M.D., Deborah A. Jackson, B.S. and Charles S. Collier, Fort Howard, Maryland.

Inhibition of Lipid Mobilization of Surgical Stress by Partially Depolymerized Hyaluronic Acid 771
By Chris J. D. Zarafonetis, M.D., Joseph Seifter, M.D., David Baeder, Ph.D., John P. Kalas, M.D. and Walter Y. M. Chang, M.D., Philadelphia and Radnor, Pennsylvania.

(Contents continued on page 14)

Luasmin

capsules and delayed action (enteric coated) tablets

Each dose contains:

Theophylline Sodium Acetate 0.2 Gm.
Ephedrine Sulfate 30 mg.
Sodium Phenobarbital 30 mg.
Supplied: Capsules and enteric coated (delayed action) tablets.
Note the adequate therapeutic dose of ephedrine balanced by the correct dose of phenobarbital.

*Ethan Allen Brown, N. E. J. Med., 223:843.
F. K. Albrecht, Mod. Mgmnt. Clin. Med. P674, Williams & Wilkins.
F. W. Wittich, J. Am. Ger. Soc., 3:239, 1955.

No dread of night for the ASTHMATIC

Keep your patient serene throughout the night, and comfortable all day too.

One capsule and one enteric-coated (delayed action) tablet at night will give your patient a full night's sleep. A capsule, two or three times a day, will complete round-the-clock relief.*

Brewer Est. 1852

Brewer & Company, Inc.
Worcester, Mass.

HYDRATES STIMULATES

Metamucil® does BOTH!

In constipation, Metamucil produces soft, easy stools and stimulates gentle peristalsis. Metamucil HYDRATES fecal matter by adsorbing and retaining water within the stool. In this way it prevents hard feces from forming, and it adds to the intestinal residue a soft, plastic bulk which STIMULATES the normal reflex activity of peristalsis.

Metamucil is a brand of psyllium hydrophilic mucilloid with dextrose.

SEARLE

PROGRESS OF MEDICAL SCIENCE

Medicine
(January and July)—G. E. Burch and William D. Love

Neurology and Psychiatry
(January and July)—F. G. Ebaugh and James Galvin

Surgery
(February and August)
I. S. Ravdin and C. G. Johnston

Ophthalmology
(February and August)
W. L. Benedict and H. P. Wagener

Preventive Medicine and Epidemiology
(March and September)
J. E. Gordon and Theodore H. Ingalls

Pathology and Bacteriology
(March and September)
Roger W. Reed and
Gardner C. McMillan

Dermatology and Syphilology
(April and October)
H. Beerman and N. R. Ingraham, Jr.

Oto-Rhino-Laryngology
(April and October)—N. D. Fabricant and A. Harry Neffson

Radiology
(May and November)—David M. Gould and John G. McAfee

Therapeutics
(May and November)
H. Gold and McKeen Cattell

Pediatrics
(June and December)—I. J. Wolman and A. M. Bongiovanni

Gynecology and Obstetrics
(June and December)
C. Bachman and Franklin L. Payne

(Contents continued on page 16)

Helps You Solve Your Clinical Problems—Quickly!

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

"The Yellow Journal"

★ Introductory Offer to New Subscribers: 8 Months for $6.

★ Special ½ Price Offer to Residents & Interns: 1 Year for $5.

Original, Authoritative Papers, plus the Monthly "Progress of Medical Science" Covering All of the Specialties

LEA & FEBIGER 600 Washington Square, Philadelphia 6, Pa.

Enclosed is $..... in payment of my subscription (as indicated below) to THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

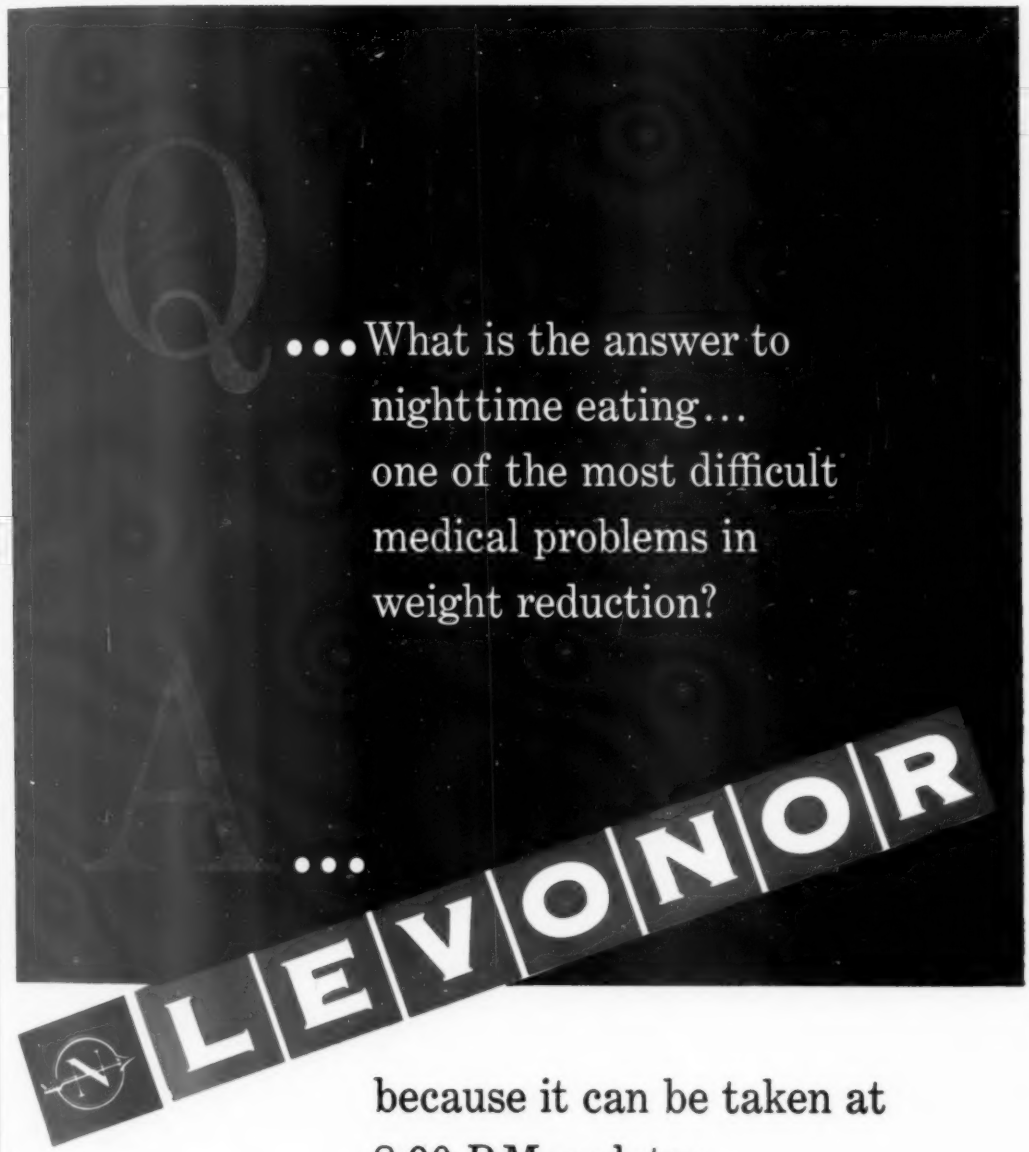
U.S. and Possessions: ☐ Special Trial Subscription, 8 months for $6.00
☐ 1 Year $10.00 ☐ 2 Years $18.00
☐ Residents and Interns Only (½ Price) 1 Year $5.00

Canada and Postal Union Countries ☐ 1 Year $10.50 All Other Countries ☐ 1 Year $12.00

NAME (print) .....

ADDRESS .....

If Intern or Resident, Give Hospital Affiliation: .....



because it can be taken at
8:00 P.M. or later
without interfering
with sleep.

administration and dosage:
Average dose: 5 to 10 mg. two or three times daily.

how supplied:
Bottles of 100 tablets, each tablet containing 5 mg. of
levo amphetamine alginate (levo 1-phenyl-2-aminopropane alginate).

LEVONOR® levo amphetamine alginate (levo 1-phenyl-2-aminopropane alginate)
Nordson. Pat. Pending.

Nordson Pharmaceutical Laboratories, Inc. · Irvington, New Jersey
(formerly Nordmark)

CONTENTS *(Continued)*

PEDIATRICS

Neonatal Hematopoiesis: A Commentary 781
By Robert D. Gens, M.D., Philadelphia, Pennsylvania.

GYNECOLOGY AND OBSTETRICS

Bacteremic Shock in Obstetrics 785
By W. Z. Bradford, Jr., M.D. and Carl Bachman, M.D., Philadelphia, Pennsylvania.

PHYSIOLOGY

Proceedings of The Physiological Society of Philadelphia, March 17, 1959 791

Book Reviews and Notices 794

"...at present, this is the oral anticoagulant of choice"[1]

HEDULIN®

NONCUMULATIVE / RAPID IN ACTION / UNIFORM IN RESPONSE
LITTLE OR NO TOXICITY / EASIER MANAGEMENT OF AMBULATORY PATIENTS

Walker LABORATORIES, INC., MT. VERNON, N. Y.

1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955.

CLINICAL NOTES

HEMATOLOGY

A NEW INTRAVENOUS IRON COMPLEX

ASTRAFER® (ASTRA) I.V.

COMPOSITION — A soluble, high-molecular, iron carbohydrate complex, equivalent to 20 mg. trivalent iron per cc., not to be confused with saccharated iron complexes.

PROPERTIES — ASTRAFER® I.V. is a neutral solution and does not irritate the intima. It is relatively free from the side reactions previously encountered with other intravenous iron preparations. 70-100% of the iron supplied by this agent is utilized in hemoglobin synthesis. Patient improvement is marked by a measurable sense of well being, and is seen coincidentally with the return to normal of serum iron and hemoglobin levels, usually beginning with the third or fourth injection.

INDICATIONS — Severe iron deficiency anemia characteristic of late pregnancy and massive or repeated blood loss, where rapid replenishment of large iron deficits is mandatory, and wherever orally administered iron may be either ineffective or poorly tolerated. To date, there is no evidence that this agent is of any value in anemias of polyarthritis or chronic nephritis. CONTRAINDICATIONS are pernicious anemia, leukemia or bone marrow depression, and liver damage.

DOSAGE — Initially, 1.5 cc. (30 mg.) to be administered slowly via the intravenous route. Patient should rest 15-30 minutes after each injection. Subsequent dosage increased according to instructions found in literature * accompanying each package.

SUPPLIED — 5 cc. color-break ampules, boxes of 10

ASTRAFER® (ASTRA) I.V.

*Further information including clinical background and detailed dosage instructions available to physicians on request.

ASTRA PHARMACEUTICAL PRODUCTS, INC.
Worcester, Mass. U. S. A.

REACHING FOR THOSE 9B's NEARLY PUT ME ON THE SHELF...

Reaching for 9B shoes and other top shelf sizes is no joke . . . it gave me a terrible kink in my back.

Before the day was over, I could hardly stoop to push a shoehorn.

I called my doctor that night and picked up the tablets he prescribed.

The pain went away fast — in just 15 minutes — and I was back on the job the next morning! But not one 9B customer came in the whole day!

Percodan®-Demi & Percodan® *Tablets*

Salts of Dihydrohydroxycodeinone and Homatropine, plus APC

FOR PAIN

ACTS FASTER—usually within 5-15 minutes. **LASTS LONGER**—usually 6 hours or more. **MORE THOROUGH RELIEF**—permits uninterrupted sleep through the night. **RARELY CONSTIPATES**—excellent for chronic or bedridden patients. **VERSATILE**—new "demi" strength permits dosage flexibility to meet each patient's specific needs. PERCODAN-DEMI provides the PERCODAN formula with one-half the amount of salts of dihydrohydroxycodeinone and homatropine.

AVERAGE ADULT DOSE: 1 tablet every 6 hours. May be habit-forming. Federal law permits oral prescription.

Each PERCODAN* Tablet contains 4.50 mg. dihydrohydroxycodeinone hydrochloride, 0.38 mg. dihydrohydroxycodeinone terephthalate, 0.38 mg. homatropine terephthalate, 224 mg. acetylsalicylic acid, 160 mg. phenacetin, and 32 mg. caffeine.

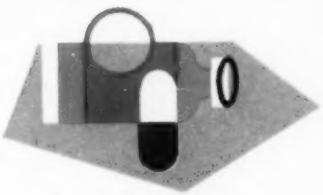
AND THE PAIN WENT AWAY FAST

Endo®

Literature? Write
ENDO LABORATORIES
Richmond Hill 18, New York

*U.S. Pat. 2,628,185

three essential steps help overweight patients eat to live, not live to eat



supervision by the physician

a balanced eating plan

supportive medication

Obedrin®

and the 60-10-70 Basic Plan

provide an effective weight control regimen

requently a patient loses weight while on a spe-ial diet, then soon gains it back again. Obedrin a valuable aid to this type of patient. It curbs nhealthy food craving while the patient estab-shes correct eating habits. Thus he becomes able *maintain* optimum weight.

Each capsule or tablet provides:

Semoxydrine® HCl (methamphetamine HCl), 5 mg., for its anorexigenic and mood-lifting effects

Pentobarbital, 20 mg., to guard against excitation

Thiamine Mononitrate, 0.5 mg., Riboflavin, 1 mg. and Nicotinic Acid (Niacin), 5 mg., to supplement the diet

Ascorbic Acid, 100 mg., to help mobilize tissue fluids

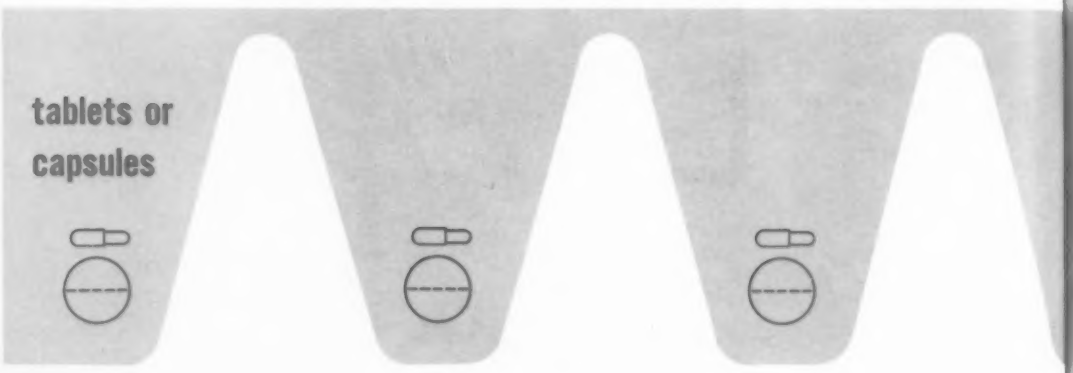
ristol, Tennessee • New York • Kansas City • San Francisco THE S. E. MASSENGILL COMPANY

for dependable

control of appetite

. . . a flexible

dosage form



The Obedrin formula permits a flexible dosage schedule which depresses the appetite when it is most important to do so—at pea hunger periods. The physician can adjust the dosage to fit each patient's need.

Obedrin

and the 60-10-70 Basic Pla

advantages of Obedrin

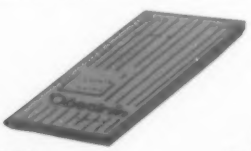
A dependable anorexigenic agent

A flexible dosage form

Minimal central nervous stimulation

Vitamins to supplement the diet

No hazards of impaction



Write for 60-10-70 menus, weight charts, and samples of Obedrin.

Used with the 60-10-7 Basic Plan, Obedrin offe an ideal weight-control reg men for the overweight patien

Bristol, Tennessee • New York • Kansas City • San Francisco THE S. E. MASSENGILL COMPAN

the house-call antibiotic

• wide range of action is reassuring when culture and sensitivity tests are impractical

• effectiveness demonstrated in more than 6,000,000 patients since original product introduction (1956)

COSA-SIGNEMYCIN®

glucosamine-potentiated tetracycline with triacetyloleandomycin

More than 90 clinical references attest to the superiority and effectiveness of Cosa-Signemycin (Signemycin). Bibliography and professional information booklet available on request.

Pfizer *Science for the world's well-being*

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc. Brooklyn 6, N. Y.

capsules
125 mg., 250 mg.

oral suspension
raspberry flavored, 2 oz. bottle, 125 mg. per teaspoonful (5 cc.)

pediatric drops
raspberry flavored, 10 cc. bottle (with calibrated dropper), 5 mg. per drop (100 mg. per cc.)

THE HEART DISEASE PATIENT NEEDS RELIEF FROM EMOTIONAL STRESS

ANXIETY INTENSIFIES the physical disorder in heart disease. "The prognosis depends largely on the ability of the physician to control the anxiety factor, as well as the somatic disease."

(Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Cardiol. 1:395, March 1958.)

TRANQUILIZATION WITH MILTOWN enhances recovery from acute cardiac episodes and makes patients more amenable to necessary limitations of activities.

(Waldman, S. and Pelner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957.)

Miltown®

meprobamate (Wallace)

Available in 400 mg. scored and 200 mg. sugar-coated tablets. Also available as MEPROSPAN* (200 mg. meprobamate *continuous release* capsules). In combination with a nitrate, for angina pectoris: MILTRATE*—(Miltown 200 mg. + PETN 10 mg.). *TRADE-MARK CM-7726

Miltown causes no adverse effects on heart rate, blood pressure, respiration or other autonomic functions.

WALLACE LABORATORIES, *New Brunswick, N. J.*

In Coronary Insufficiency . . .

Your high-strung angina patient often expends a "100-yd. dash" worth of cardiac reserve through needless excitement.

Curbs emotion as it boosts coronary blood supply

CONTROL OF EMOTIONAL EXERTION with Miltrate leaves him more freedom for physical activity.

IMPROVED CORONARY BLOOD SUPPLY with Miltrate increases his exercise tolerance.

Miltrate*

Miltown® (*meprobamate*) + PETN

Each tablet contains: 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

Supplied: Bottles of 50 tablets.

Usual dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime. Dosage should be individualized.

WALLACE LABORATORIES · *New Brunswick, N. J.*

CML-9199-59 *TRADE-MARK

the
"full-range"
oral
hypoglycemic
agent

DBI

Trademark, brand of Phenformin

in the management of mild,
moderate and severe diabetes
(juvenile and adult)

DBI (N^1-β-phenethylbiguanide HCl) is an entirely new oral hypoglycemic compound, different in chemical structure, mode of action, and in spectrum of activity from the sulfonylureas. DBI is usually effective in low dosage range (50 to 150 mg. per day).

"full-range" hypoglycemic action – DBI lowers elevated blood-sugar and eliminates glycosuria in **mild, moderate** and **severe** diabetes mellitus . . .

brittle diabetes, juvenile or adult – DBI combined with injected insulin improves regulation of the diabetes and helps prevent the wide excursions between hypoglycemic reactions and hyperglycemic ketoacidosis.

stable adult diabetes – satisfactory regulation of diabetes is often achieved with DBI alone without the necessity for insulin injections.

juvenile diabetes – DBI often permits a reduction as great as 50 per cent or more in the daily insulin requirement.

primary and secondary sulfonylurea failures – DBI alone, or in conjunction with a sulfonylurea, often permits satisfactory regulation of diabetes in patients who have failed to respond initially or who have become resistant to oral sulfonylurea therapy.

smooth onset – less likelihood of severe hypoglycemic reaction – DBI has a smooth, gradual blood-sugar lowering effect, reaching a maximum in from 5 to 6 hours, and a return to pre-treatment levels usually in 10 to 12 hours.

safety – daily use of DBI in therapeutic dosage for varying periods up to 2½ years has produced no clinical toxicity.

side reactions – side reactions produced by DBI are chiefly gastrointestinal and occur with increasing frequency at higher dosage levels (exceeding 150 mg. per day). Anorexia, nausea or vomiting may occur – but these symptoms abate promptly upon reduction in dose or withdrawal of DBI.

supplied – DBI, 25 mg. scored, white tablets – bottle of 100.

IMPORTANT – before prescribing DBI the physician should be thoroughly familiar with general directions for its use, indications, dosage, possible side effects, precautions and contraindications, etc. Write for complete detailed literature.

an original development from the research laboratories of

u.s. vitamin & pharmaceutical corporation

Arlington-Funk Laboratories, division
250 East 43rd Street, New York 17, N. Y.

in
bronchial
asthma
Decadron®
DEXAMETHASONE
treats more patients more effectively
a new order of magnitude in corticosteroid effectiveness
a new order of magnitude in margin of safety
A dramatic pattern of good to excellent improvement is reported with DECADRON in 90 percent of 153 patients† with acute, chronic and emphysematous bronchial asthma. †Analysis of Clinical Reports.
DECADRON is a trademark of Merck & Co., Inc.
MSD
MERCK SHARP & DOHME
DIVISION OF MERCK & CO., Inc., PHILADELPHIA 1, PA.

RELIEVES ANXIETY IN HYPERTENSIVE PATIENTS *without producing depression*

Miltown relieves mental pressure which often aggravates symptoms of hypertension and impairs effectiveness of antihypertensive therapy.

Combined with specific therapy, Miltown provided greater over-all improvement in hypertensive patients than antihypertensive therapy alone.[1,2] In 58 patients receiving combined therapy, over 90% (including moderate and severe cases) benefited from relief of headache, nervousness, palpitations, insomnia, weakness and dizziness.[1,2]

Miltown was found "a useful adjunct in the treatment of the psychogenic and neurogenic components of hypertension."[3]

Miltown®

meprobamate (Wallace)

- does not cause depression
- does not interfere with heart rate, blood pressure, respiration, G.I. function or other autonomic mechanisms

1. Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: Am. J. M. Sc. 234:150, Aug. 1957. 2. Dunsmore, R. A., Dunsmore, L. D., Bickford, A. F. and Goldman, A.: Am. J. M. Sc. 233:280, March 1957. 3. Boyd, L. J., Huppert, V. F., Mulinos, M. G. and Hammer, H.: Am. J. Cardiol. 3:229, Feb. 1959.

SUPPLIED: 400 mg. scored and 200 mg. sugar-coated tablets in bottles of 50. Also available as MEPROSPAN* (Miltown *continuous release* capsules).

*TRADE-MARK

Literature and samples on request.

CM-9204

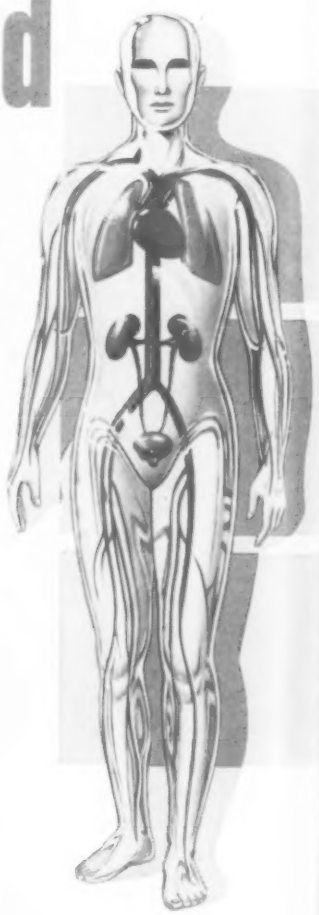
WALLACE LABORATORIES • *New Brunswick, N. J.*

NEW

HYDRODIURIL™

(HYDROCHLOROTHIAZIDE)

simplifies* and improves any regimen for hypertension



*it's as easy as 1, 2, 3 to use

HYDRODIURIL

(HYDROCHLOROTHIAZIDE)

1 Initiate therapy with HYDRODIURIL: one 25 mg. tablet or one 50 mg. tablet once or twice a day. HYDRODIURIL by itself often causes an adequate drop in blood pressure over a period of two to three weeks. This may be all the therapy some patients require.

2 Add or adjust other agents as required: HYDRODIURIL enhances the activity of all commonly-used antihypertensive agents; thus, the dosage of other medication (rauwolfia, reserpine, hydralazine, veratrum) should be initiated or adjusted as indicated by patient condition. If a ganglion-blocking agent is contemplated or being used, usual dosage must be reduced by 50 per cent.

3 Adjust dosage of all medication: the patient must be frequently observed and careful adjustment of all agents should be made to establish optimal maintenance dosage.

Supplied: 25 mg. and 50 mg. scored tablets HYDRODIURIL (Hydrochlorothiazide) bottles of 100 and 1,000.
Additional literature for the physician is available on request.

HYDRODIURIL is a trademark of Merck & Co., Inc. Trademarks outside the U. S.: DICHLOTRIDE, DICLOTRIDE, HYDROSALURIC

MSD MERCK SHARP & DOHME, Division of Merck & Co., Inc., Philadelphia 1, Pa.

The more potent

the greater the need for

Physiologic Balance[1]

start...alternate...terminate

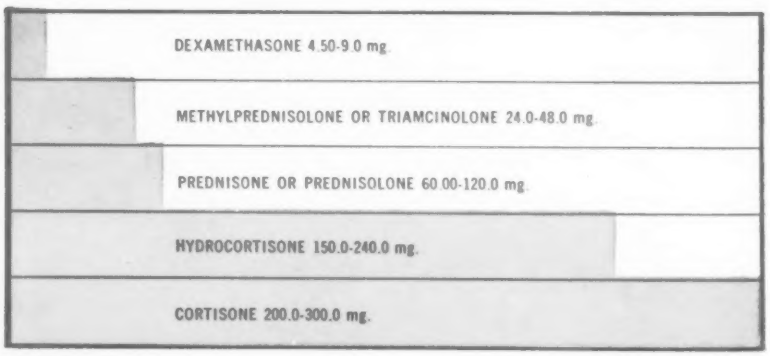
with potent, long-acting, intramuscular

Cortrophin®

the specific, physiologic adrenocortical stimulant

Balance corticosteroid therapy with Cortrophin-Zinc...

After every 6 days' SYSTEMIC THERAPY WITH:



On the 7th day OMIT THE CORTICOSTEROID AND INJECT CORTROPHIN-ZINC, 40 U.S.P. UNITS, I.M.

the systemic corticosteroid . . .

(even in short-term therapy)

-Zinc

corticotropin-alpha zinc hydroxide (ORGANON)

To minimize adrenal suppression and atrophy from corticosteroid therapy, repository corticotropin "may be given periodically, and particularly when corticoid withdrawal is started."

(Report to A.M.A. Council on Drugs: J.A.M.A. **169**:1063, 1959)

- **Stimulate the adrenal cortex**
- **Maintain resistance to stress**
- **Avoid post-therapy adrenal insufficiency**

CORTROPHIN-ZINC: 40 or 20 U.S.P. units/cc., 5-cc. vials, 1-cc. sterile, disposable syringes. "Produces a more prolonged hormone effect . . . more potent and longer acting than gel ACTH . . . a free flowing substance that can be injected in a very small gauge needle."[2]

1. Krusius, F. E., and Oka, M.: Ann. Rheumat. Dis. *17*:184, 1958. 2. Siegel, S. C.: Lederle Symposium Report, *1*:43, 1958.

Organon

Organon Inc., Orange, New Jersey

100

a significant *Sanborn achievement in electrocardiographs*

VISO

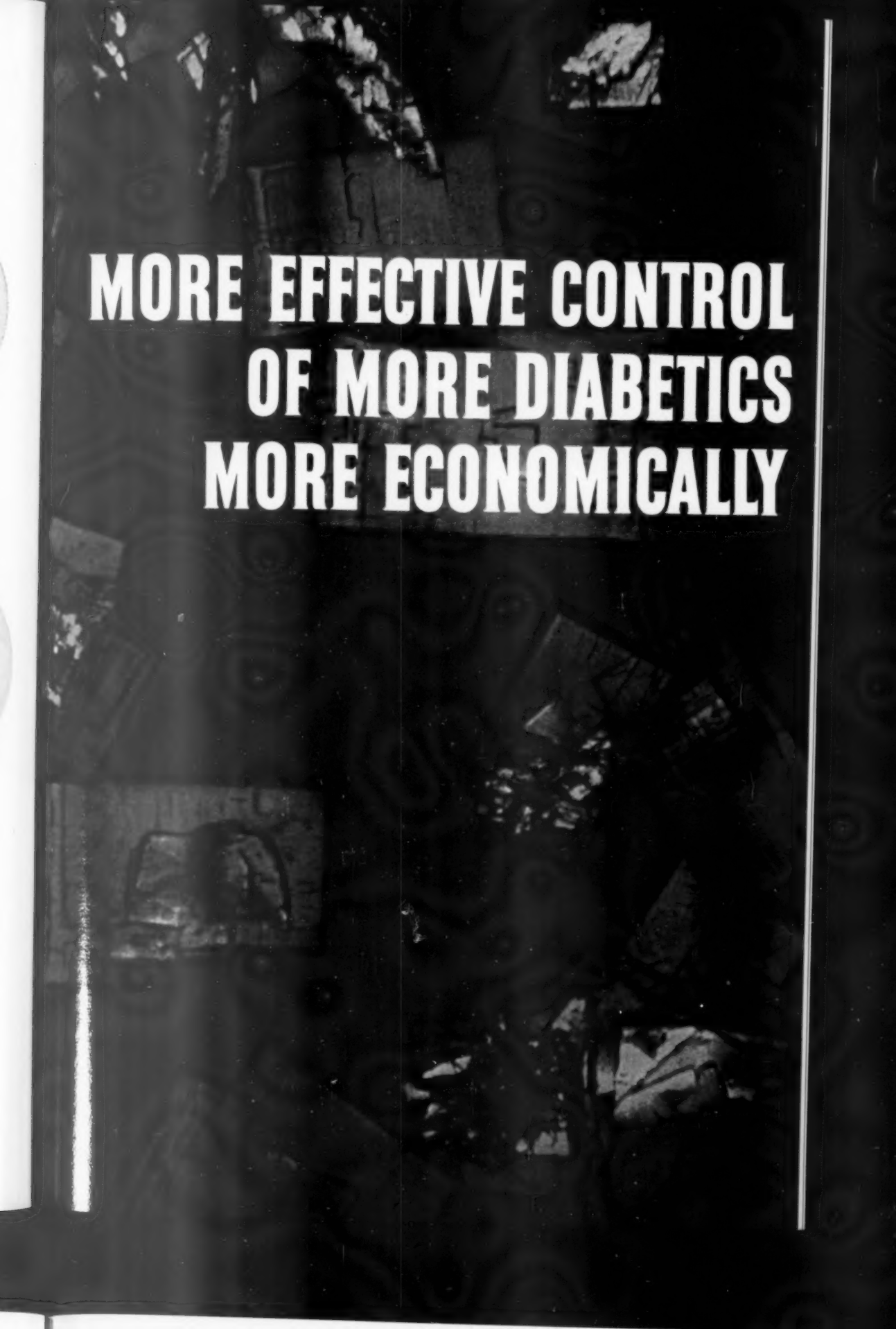
the completely new, 2-speed

SANBORN Model 100 VISO-CARDIETTE

Here is an electrocardiograph in which *no detail* has been overlooked to give you diagnostically *accurate* information ... the greatest possible operating *convenience* ... and modern, *functional* attractiveness. With thirty-five years of experience, this is the finest electrocardiograph Sanborn Company has ever produced. Priced at eight hundred fifty dollars, delivered continental U. S. A.

SANBORN COMPANY

MEDICAL DIVISION • 175 Wyman St., Waltham 54, Mass.


MORE EFFECTIVE CONTROL
OF MORE DIABETICS
MORE ECONOMICALLY

MORE EFFECTIVE CONTROL OF MORE DIABETICS MORE ECONOMICALLY

DIABINESE

brand of chlorpropamide

tablets / once-a-day dosa

The specific pharmacologic properties of DIABINESE—high activity...freedom from metabo degradation...gradual excretion—permit (1) prompt lowering of elevated blood sugar lev without a "loading" dose, and (2) smooth, sustained maintenance devoid of marked blo sugar fluctuations—on convenient, *lower-cost,* once-a-day dosage. This is the consensus extensive clinical literature.[1-11]

More than two years of clinical experience with DIABINESE have demonstrated effective contr of a *larger percentage* of "maturity-onset" diabetics—smoother control of patients on pre ous oral therapy—usefulness as "a valuable adjunct to the therapy of brittle and poo controlled diabetics,"[1] generally with decreased insulin requirements—and control in *over per cent of patients who have become refractory to other oral agents.* Widespread use DIABINESE since its introduction has confirmed the low incidence of side effects reported by t original investigators.

Thus, DIABINESE merits *first consideration* for any diabetic presently receiving or potentiall better managed with oral therapy—including many diabetics for whom previous oral agen have proved ineffective.

Supplied: Tablets, white, scored, 250 mg., bottles of 60 and 250; 100 mg., bottles of 100.

PROFESSIONAL LITERATURE AVAILABLE ON REQUEST

Science for the world's well-being

Pfizer

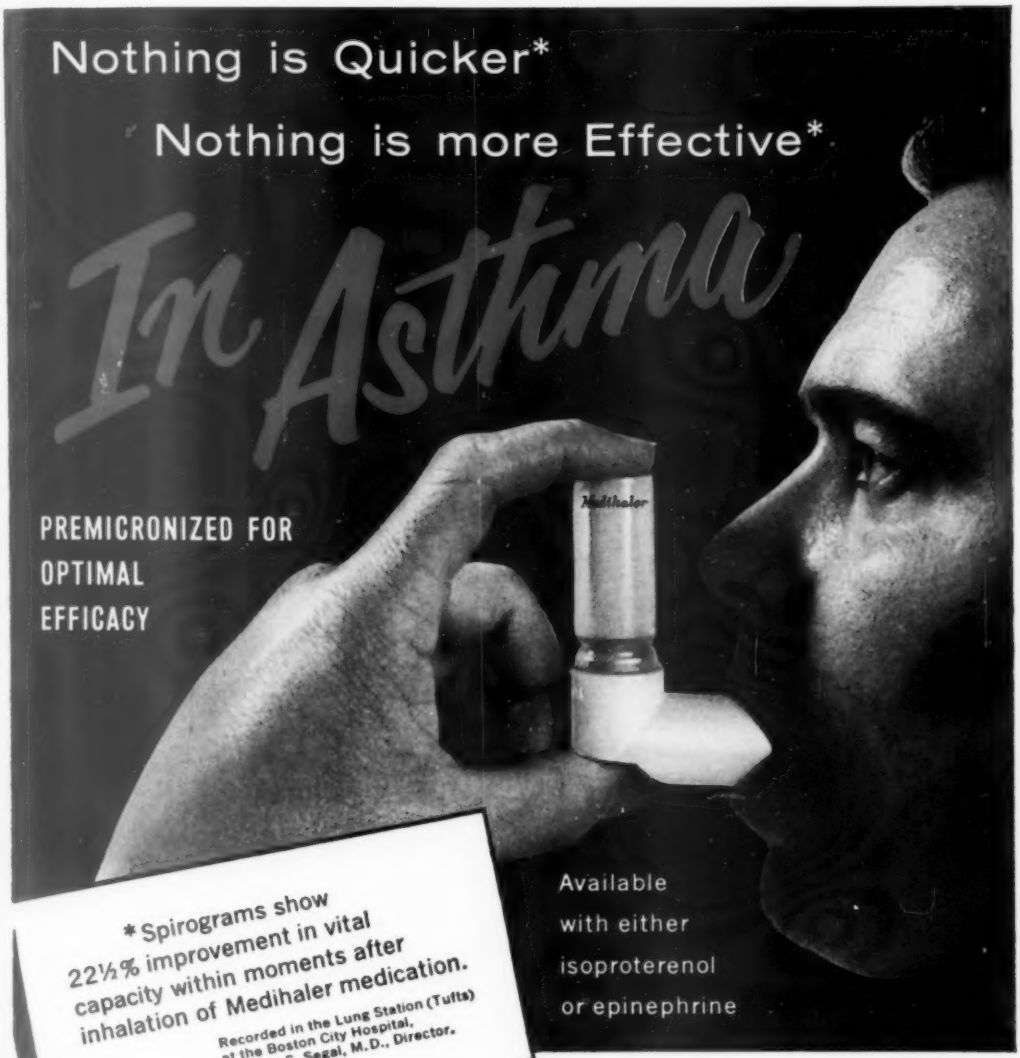
PFIZER LABORATORIES, Brooklyn 6, N. Y.
Division, Chas. Pfizer & Co., Inc.

1. Dobson, H., et al.: Ann. New York Acad. Sc. 74:940, 1959. 2. Greenhouse, B.: Paper presented at Conference on Diabinese and Diabetes Mellitus, New York Acad. Sc., Sept. 25-27, 1958, New York, N.Y. 3. Forsham, P. H.; Magid, G. ... and Dorosin, D. E.: Ibid., p. 672. 4. Beaser, S. B.: Ibid., p. 701; New Engl... J. Med. 259:573, 1958. 5. Bloch, J., and Lenhardt, A.: Ann. New York Acad. Sc. 74:954, 1958. 6. O'Driscoll, B. J.: Lancet 2:749, 1958. 7. Hadley, W. B.; Khachadurian, A., and Marble, A.: Ann. New York Acad. Sc. 74:621, 1959. 8. Duncan, G. G.; Schless, G. L., and Demeshkieh, M. M. A.: Ibid., p. 717. Handelsman, M. B.; Levitt, L., and Calabretta, M. F.: Ibid., p. 632. 10. Hill, A. G., and Abelove, W. A.: Ibid., p. 845. 11. Drey, N. W., et al.: Ibid., p. 962.

Nothing is Quicker*

Nothing is more Effective*

In Asthma



PREMICRONIZED FOR OPTIMAL EFFICACY

*Spirograms show 22½% improvement in vital capacity within moments after inhalation of Medihaler medication.

Recorded in the Lung Station (Tufts) at the Boston City Hospital, Maurice S. Segal, M.D., Director.

Available with either isoproterenol or epinephrine

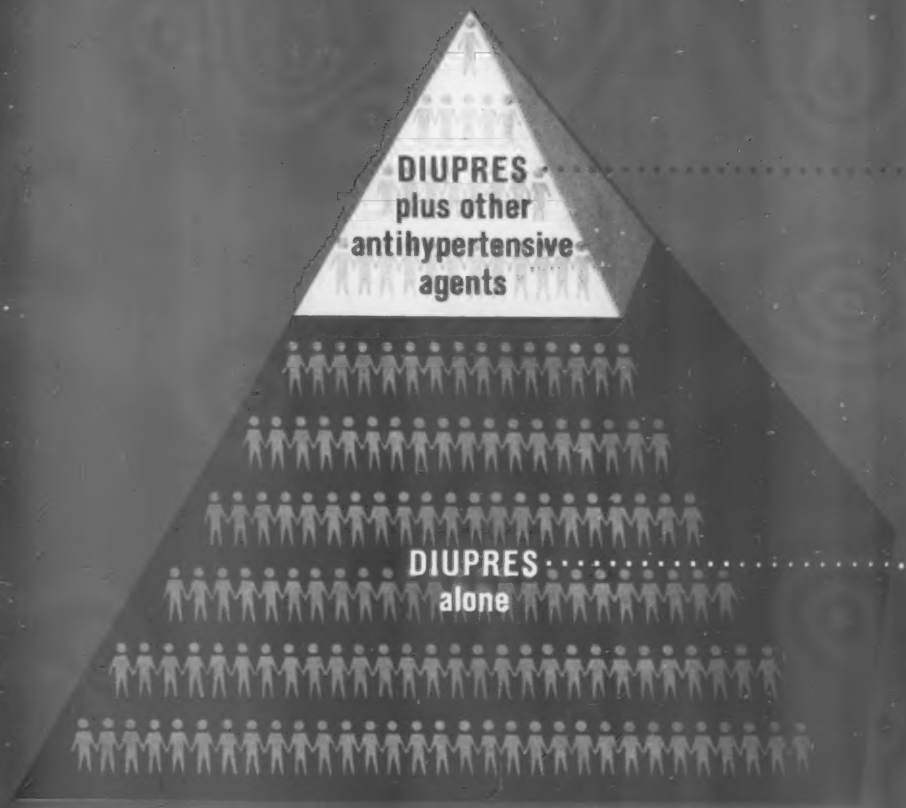
Automatically measured-dose aerosol medications.
Nonbreakable...Shatterproof
Spillproof...Leakproof

Medihaler-ISO® Isoproterenol sulfate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.06 mg. isoproterenol.

Medihaler-EPI® Epinephrine bitartrate, 7.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.15 mg. epinephrine.

NOTABLY WELL TOLERATED AND EFFECTIVE FOR CHILDREN, TOO

Riker Northridge, Calif.



DIUPRES PROVIDES "BROAD-BASE" ANTIHYPERTENSIVE THERAPY

... is effective by itself in a majority of patients with mild or moderate hypertension, and even in many with severe hypertension

greatly improved
and simplified management
of
hypertension

DIUPRES*

DIURIL® WITH RESERPINE

the first "wide-range" antihypertensive—effective in mild, moderate, and severe hypertension

- more hypertensives can be better controlled with DIUPRES alone than with any other agent . . . with greater simplicity and convenience, and with decreased side effects
- can be used as total therapy or primary therapy, adding other drugs if necessary
- in patients now treated with other drugs, can be used as replacement or adjunctive therapy
- should other drugs need to be added, they can be given in much lower than usual dosage so that their side effects are often strikingly reduced
- organic changes of hypertension may be arrested and reversed . . . even anginal pain may be eliminated
- patient takes one tablet rather than two . . . dosage schedule is easy to follow
- economical

DIUPRES-500 500 mg. DIURIL (chlorothiazide), 0.125 mg. reserpine. One tablet one to three times a day.

DIUPRES-250 250 mg. DIURIL (chlorothiazide), 0.125 mg. reserpine. One tablet one to four times a day.

MSD MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

*DIUPRES AND DIURIL (CHLOROTHIAZIDE) ARE TRADEMARKS OF MERCK & CO., INC.

both blood picture and patient respond to TRINSICON®

Investigators[1,2] have determined that low serum iron may be accompanied by insidious vitamin B_{12} deficiencies which result from subnutrition, increased demand, or lack of intrinsic factor. Coexisting vitamin C deficiencies also have been found.[3]

These studies suggest that an anemia may be multiple in nature—that optimum results would be derived from a combination of therapeutic agents.

Trinsicon offers therapeutic quantities of all known hematinic factors. Prescribe two Pulvules® daily to provide assured response in all treatable anemias.

Trinsicon® (hematinic concentrate with intrinsic factor, Lilly)

1. A. M. A. Arch. Int. Med., *99*:346, 1957.
2. Am. J. Obst. & Gynec., *70*:1309, 1955.
3. Lancet, *1*:448, 1957.

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

919033

in vaginitis

IMPROVED

TRICOFURON®

destroys all **3** *principal pathogens*

Whether vaginitis is caused by Trichomonas, Monilia or Hemophilus vaginalis—alone or combined—TRICOFURON IMPROVED swiftly relieves symptoms and malodor, and achieves a truly high percentage of cultural cures, frequently in 1 menstrual cycle. TRICOFURON IMPROVED provides: a *new* specific moniliacide MICOFUR® brand of nifuroxime, the *established* specific trichomonacide FUROXONE® brand of furazolidone and the *combined* actions of both against Hemophilus vaginalis.

1. *Office* insufflation once weekly of the Powder (MICOFUR [*anti*-5-nitro-2-furaldoxime] 0.5% and FUROXONE 0.1% in an acidic water-soluble powder base). **2.** Continued *home* use twice daily, with the Suppositories (MICOFUR 0.375% and FUROXONE 0.25% in a water-miscible base).

℞ NEW BOX OF 24 SUPPOSITORIES WITH APPLICATOR FOR MORE PRACTICAL AND ECONOMICAL THERAPY.

NITROFURANS—a *new* class of antimicrobials—neither antibiotics nor sulfonamides.

EATON LABORATORIES, NORWICH, NEW YORK

the flavor of fruit
and a broad spectrum antibiotic

SUMYCIN

TETRACYCLINE

syrup / aqueous drops

new Sumycin Syrup

An aqueous tetracycline suspension, phosphate potentiated, containing 125 mg. tetracycline (hydrochloride equivalent) per 5 cc. teaspoonful.

60 cc. bottles

new Sumycin Aqueous Drops

An aqueous tetracycline suspension, phosphate potentiated, containing 100 mg. tetracycline (hydrochloride equivalent) per cc.

10 cc. bottles with the new, unbreakable 'FLEXIDOSE' DROPPER

. . . delicious aqueous suspensions to assure patient acceptance for effective tetracycline therapy . . . children especially will like their tasty fruit flavor

Also available:	Tetracycline phosphate complex equiv. to tetracycline HCl (mg.)	Packaging:
Sumycin Capsules	250 mg. per capsule	Bottles of 16 and 100
Sumycin Half Strength Capsules	125 mg. per capsule	Bottles of 16 and 100
Sumycin Intramuscular with Xylocaine*	250 mg. per vial	1 dose vials
Sumycin Intramuscular with Xylocaine*	100 mg. per vial	1 dose vials

SQUIBB *Squibb Quality — the Priceless Ingredient*

'SUMYCIN'® AND 'FLEXIDOSE' ARE SQUIBB TRADEMARKS *T.M. © ASTRA PHARMACEUTICAL PRODUCTS, INC. FOR LIDOCAINE

PMB 200

"PREMARIN"® WITH MEPROBAMATE

FOR PROVEN MENOPAUSAL BENEFITS

The vast majority of menopausal women, **especially on the first visit,** are nervous, apprehensive, and tense. PMB-200 or PMB-400 gives your patient the advantage of **extra** relief from anxiety and tension, particularly when the patient is "high strung," under prolonged emotional stress, or when psychogenic manifestations are acute. Proven menopausal benefits are confirmed by the wide clinical acceptance of "Premarin," specifically for the relief of hot flushes and other symptoms of estrogen deficiency, together with the well established tranquilizing efficacy of meprobamate.

Two potencies that will meet the needs of your patients: **PMB-200** — Each tablet contains conjugated estrogens equine ("Premarin") 0.4 mg., and 200 mg. of meprobamate. When greater tranquilization is necessary you can prescribe **PMB-400** — Each tablet contains conjugated estrogens equine ("Premarin") 0.4 mg., and 400 mg. of meprobamate. Both potencies are available in bottles of 60 and 500.

Ayerst Laboratories New York16,N.Y.
Montreal, Canada

Meprobamate, licensed under U.S. Pat. No. 2,724,720

5916

Victim of Overeating and "Oversitting"

℞

BIPHETAMINE®

A 'STRASIONIC' RELEASE ANORETIC RESIN

- **10-14 Hour Appetite Curb**
- **10-14 Hour Mild Invigoration**
- **Predictable Weight Loss...**
  a comfortable 1 to 3 lbs. a week in 9 out of 10 cases

In many instances both appetite limitation and mild invigoration ('Biphetamine') are required to effect the balance between caloric intake and energy output necessary for predictable weight reduction and control. Since 'Strasionic' release is employed, the desired therapeutic action is uniform, predictable and comfortable.

Biphetamine may be prescribed for obese patients who are hypertensive, arthritic, diabetic, pregnant, menopausal, aged; and to reduce surgical risks. Use with initial care in patients hypersensitive to sympathomimetic compounds, in cases of coronary disease or severe hypertension.

- **Single Capsule Daily Dose 10 to 14 hours before retiring**

3 STRENGTHS

List No. 875
BIPHETAMINE® '20' Resin
Each black capsule contains:
d-amphetamine ..... 10 mg.
dl-amphetamine ..... 10 mg.
as resin complexes

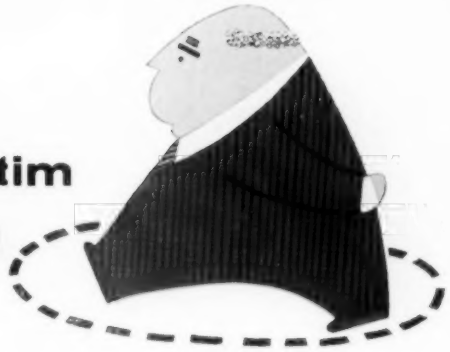
List No. 878
BIPHETAMINE® '12½' Resin
Each black and white capsule contains:
d-amphetamine ..... 6.25 mg.
dl-amphetamine ..... 6.25 mg.
as resin complexes

List No. 895
BIPHETAMINE® '7½' Resin
Each white capsule contains:
d-amphetamine ..... 3.75 mg.
dl-amphetamine ..... 3.75 mg.
as resin complexes

℞ Only. Caution: Federal law prohibits dispensing without prescription.

STRASENBURGH LABORATORIES
ROCHESTER, N.Y., U.S.A.

Originators of 'Strasionic' (sustained ionic) Release



Victim of Overeating

℞ NEW

Non-Amphetamine

IONAMIN™

A 'STRASIONIC' ANORETIC

PHENYL-*TERT.*-BUTYLAMINE RESIN

- **10-14 Hour Appetite Curb**
- **Predictable Weight Loss...**
  a comfortable .221 lbs. per day in average case

In many instances, appetite limitation only ('Ionamin') is required to effect the balance between caloric intake and energy output necessary for predictable weight reduction and control. Since 'Strasionic' release is employed, the desired therapeutic action is uniform, predictable and comfortable.

Ionamin may be prescribed for obese patients who are arthritic, diabetic, pregnant, menopausal, aged, to reduce surgical risks, and may be used with caution in hypertensive or cardiovascular disease.

- **Single Capsule Daily Dose 10 to 14 hours before retiring**

2 STRENGTHS

List No. 904

IONAMIN™ '30'

Each yellow capsule contains:
phenyl-tert.-butylamine .. 30 mg.
as a resin complex

List No. 903

IONAMIN™ '15'

Each grey and yellow capsule contains:
phenyl-tert.-butylamine .. 15 mg.
as a resin complex

Rx Only.
Caution: Federal law prohibits dispensing without prescription.

STRASENBURGH LABORATORIES
ROCHESTER, N.Y., U.S.A.

Originators of 'Strasionic' (sustained ionic) Release

•VALUABLE NEW HOEBER BOOKS FOR THE CLINICIAN

HOOBLER'S Hypertensive Disease

NEW! Here in one book is a complete summary of the details of diagnosis and management of all forms of elevated blood pressure, whether primary or secondary to other diseases. Contains 12 appendices designed to give precise working details of various tests and treatment regimens.

By SIBLEY HOOBLER, M.D., *University of Michigan Hospital. 364 pp. $7.50*

LAWRENCE'S Cellular and Humoral Aspects of the Hypersensitive States

25 AUTHORITIES from a variety of disciplines bring together in one source the diverse approaches to those aspects of immunology relating to altered tissue reactivity. Everyone concerned with the problems of hypersensitivity will welcome this valuable new addition to medical literature.

By 25 Authors. Edited by H. SHERWOOD LAWRENCE, M.D., *New York University. 683 pp., 192 illus. $18.00*

PALMER'S Clinical Gastroenterology

BEDSIDE MEDICINE. Diagnosis and therapy with recommendations based on personal experience and especially prepared clinical illustrations. By one of the country's most thoughtful and original gastroenterologists.

By EDDY D. PALMER, M.D., *Lieut. Col. U.S.A.; formerly Chief of Gastroenterology, Walter Reed Hospital. 640 pp., profusely illus. $18.50*

PAUL B. HOEBER, Inc., *publishers*
MEDICAL BOOK DEPARTMENT OF HARPER & BROTHERS, 49 East 33rd Street, New York 16, N.Y.

Please send me *on approval:*

☐ HOOBLER'S Hypertensive Disease ..... $ 7.50
☐ LAWRENCE'S Hypersensitive States $18.00
☐ PALMER'S Clinical Gastroenterology $18.50

☐ My check is enclosed (return privileges) ☐ Bill me

Name .....

Address ..... *City* ..... *State* .....

AJMS 6/59

New... for the metabolic treatment of

gout

ANTURAN™

(sulfinpyrazone GEIGY)

High Potency Uricosuric Agent

By significantly increasing renal excretion of urate and thus lowering plasma uric acid, the new highly potent uricosuric agent ANTURAN strikes directly at the basic metabolic defect in gout.

Exceptionally high potency...4 to 6 times that of probenecid ...is the outstanding characteristic of ANTURAN. The effectiveness of ANTURAN is retained indefinitely and tolerance to it is good.

Clinically, ANTURAN:

- Prevents formation of new tophi
- Causes gradual absorption of old tophi
- Relieves chronic pain
- Restores joint mobility

ANTURAN is not designed for the treatment of acute attacks for which BUTAZOLIDIN® IS recommended. **Detailed Information On Request**

Yu, T. F., Burns, J. J., and Gutman, A. B. Arth. & Rheumat. 1:532, 1958.

ANTURAN (sulfinpyrazone GEIGY). Scored tablets of 100 mg. in bottles of 100.

BUTAZOLIDIN® (phenylbutazone GEIGY)

Geigy

Ardsley, New York

THE JOURNAL OF THE INTERNATIONAL COLLEGE OF SURGEONS

Official monthly publication of the International College of Surgeons

Edited by Dr. Max Thorek

Publications Committee

Francisco Graña, M.D., *Chairman*
Rudolph Nissen, M.D.
Henry W. Meyerding, M.D.
Max Thorek, M.D., *Editor-in-Chief*
Arnold S. Jackson, M.D.
Edward L. Compere, M.D.

Summary Editors

Dr. Manuel A. Manzanilla, Jr., Mexico, D.F.
Spanish

Dr. Virgilio Alves de Carvalho Pinto,
São Paulo, Brazil
Portuguese

Dr. Fritz Rothbart, Chicago, Illinois
German

Dr. Antonello Franchini and
Dr. Martin Mini, Bologna, Italy
Italian

M. Edwin Fawer
Geneva, Switzerland
French

Its pages are open to all surgeons, regardless of membership in the International College of Surgeons

Summaries of all articles in five languages

Annual Subscription, $14.50.

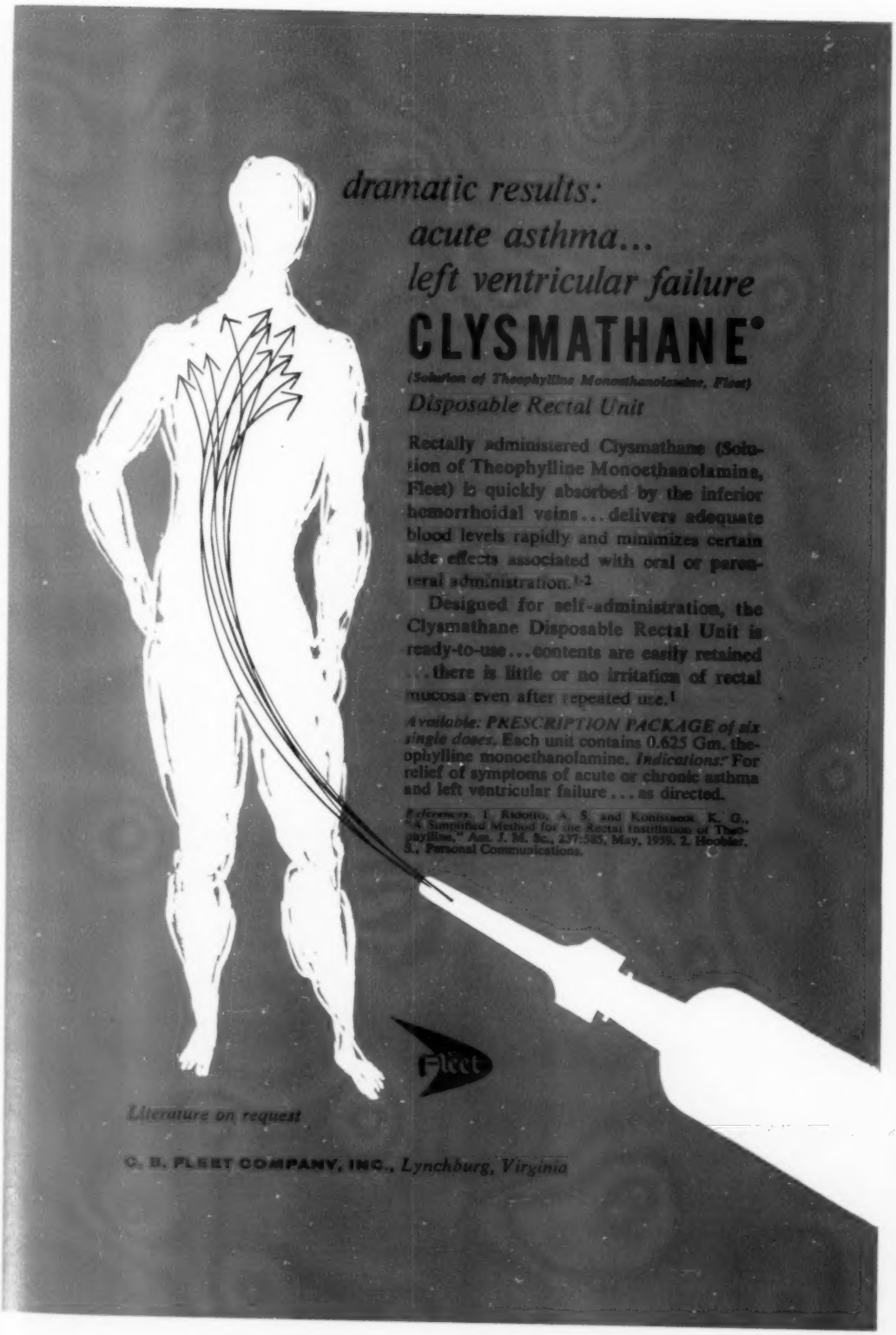
REQUEST FOR SAMPLE COPY

A complimentary copy of the Journal will be sent without obligation.

Please send us the name and address on a post card or your professional letterhead.

Mail request to:

Journal, International College of Surgeons (Circulation Office), Coliseum Tower, 10 Columbus Circle, New York 19, New York.


dramatic results:
acute asthma...
left ventricular failure
CLYSMATHANE®
(Solution of Theophylline Monoethanolamine, Fleet)
Disposable Rectal Unit
Rectally administered Clysmathane (Solution of Theophylline Monoethanolamine, Fleet) is quickly absorbed by the inferior hemorrhoidal veins... delivers adequate blood levels rapidly and minimizes certain side effects associated with oral or parenteral administration.[1-2]
Designed for self-administration, the Clysmathane Disposable Rectal Unit is ready-to-use... contents are easily retained ...there is little or no irritation of rectal mucosa even after repeated use.[1]
Available: PRESCRIPTION PACKAGE of six single doses. Each unit contains 0.625 Gm. theophylline monoethanolamine. Indications: For relief of symptoms of acute or chronic asthma and left ventricular failure ... as directed.
References: 1. Rikoto, A. S. and Konisteos, K. G., "A Simplified Method for the Rectal Instillation of Theophylline," Am. J. M. Sc., 237:585, May, 1959. 2. Heubler, S., Personal Communications.
Fleet
Literature on request
C. B. FLEET COMPANY, INC., Lynchburg, Virginia

New and comprehensive survey of the basic facts . . .

Robinson and Robinson: CLINICAL DERMATOLOGY FOR STUDENTS AND PRACTITIONERS

"During World War II there was a rebirth of interest in dermatology. It became apparent to those interested in this field that a dermatologist must not be solely dependent on a casual visual examination but must study the entire patient in order to arrive at a definite diagnosis. The diagnostician should not be content with the clinical impression afforded by morphologic skin changes, but, through experience gained by years of study and practice, must correlate laboratory findings and clinical symptoms.

"The skin is not only a protective covering but is a functioning organ which has nervous, vascular, and hormonal communications with the viscera, central nervous system and the vascular system. It is the largest organ in the human body and frequently reflects disturbances in normal physiological functions, or pathologic changes elsewhere in the body.

"The art of diagnosis applied to dermatology requires careful inspection of the patient by the examining physician and a detailed record of abnormal findings. The major portion of the book is devoted to a discussion of the morphologic appearances of the more common dermatoses, methods of diagnosis, the relationship of cutaneous lesions to systemic diseases, and suggestions for treatment. Brief mention is made of the more uncommon dermatoses."—*Preface*

By HARRY. M. ROBINSON, JR., *B.S., M.D., Professor of Dermatology and Head of the Division of Dermatology, University of Maryland School of Medicine; Chief Dermatologist, University Hospital; and* RAYMOND C. V. ROBINSON, *M.S., M.D., M.Sc. (Med.), Associate Professor of Dermatology, University of Maryland School of Medicine; Assistant Chief of Dermatology Clinic, University Hospital.*

June 1959 • 250 pp., 117 figs. • $8.50

Publishers of Medical and Scientific Books and Periodicals

SANS TACHE

WILLIAMS & WILKINS COMPANY

BALTIMORE 2, MD.

SHOP BY MAIL

THE WILLIAMS AND WILKINS COMPANY
Baltimore 2, Md.

Please send the following on approval:

Name _____ (Please print)

Address _____

City _____ Zone _____ State _____

☐ Payment enclosed. ☐ Bill me.

Shopping by mail is an easy, time-saving way to select books for your personal library.

AJMS 6–59

around the clock ulcer control with **B.I.D.** *dosage*

Just one 10 mg. Daricon tablet in the morning, and one at night before retiring, keeps your patient free from the pain and discomfort caused by gastrointestinal spasm, hypermotility, and hypersecretion.

Daricon is a remarkably potent and well tolerated antisecretory/antimotility agent. Its *naturally* prolonged action provides day and night relief of pain and symptoms associated with peptic ulcer, functional bowel syndrome, biliary tract dysfunctions, ulcerative colitis, and other gastrointestinal disorders characterized by spasm, hypermotility, and hypersecretion.

Dosage: 10 mg. b.i.d. (morning and evening).

EVEN REFRACTORY CASES RESPOND

new **DARICON**•

Pfizer *Science for the world's well-being*

Pfizer Laboratories
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

References: 1. Finkelstein, M., et al.: J. Pharmacol. & Exper. Therap. 125:330 (April) 1959. 2. McHardy, G., et al.: Postgrad. Med., in press. 3. Winkelstein, A.: Amer. J. Gastroenterol., in press. 4. Finkelstein, M., et al.: Presented at Fall Meeting, Amer. Soc. Pharmacol. & Exper. Therap., 1958. 5. Leming, B.: Clin. Med. 6:423 (March) 1959.

•Trademark

NOW

. . . a new way to relieve pain and stiffness in muscles and joints

INDICATED IN:

MUSCLE STIFFNESS

LUMBOSACRAL STRAIN

SACROILIAC STRAIN

WHIPLASH INJURY

BURSITIS

SPRAINS

TENOSYNOVITIS

FIBROSITIS

FIBROMYOSITIS

LOW BACK PAIN

DISC SYNDROME

SPRAINED BACK

"TIGHT NECK"

TRAUMATIC STRAINS AND BRUISES

POSTOPERATIVE MYALGIA

■ Exhibits unusual analgesic properties, different from those of any other drug ■ Specific and superior in relief of SOMAtic pain ■ Modifies central perception of pain without abolishing natural defense reflexes ■ Relaxes abnormal tension of skeletal muscle

SOMA™

N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate

■ More specific than salicylates ■ Less drastic than steroids ■ More effective than muscle relaxants

SOMA has an unique analgesic action. It apparently modifies central pain perception without abolishing peripheral pain reflexes. SOMA is particularly effective in relieving joint pain. Patients say that they feel better and sleep better with SOMA than with any previously used analgesic, sedative or relaxant drug.
SOMA also relaxes muscle hypertonia, with its stresses on related joints, ligaments and skeletal structures.

ACTS FAST. Pain-relieving and relaxant effects start in 30 minutes and last 6 hours.

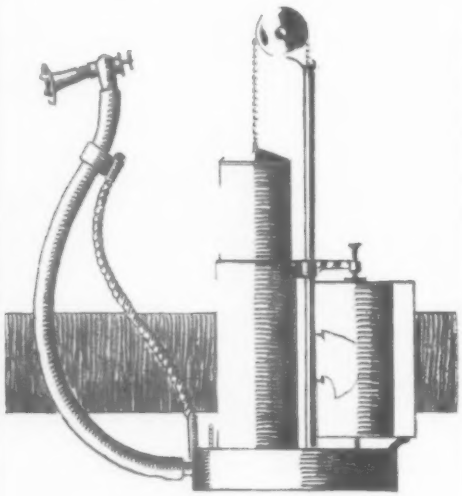
NOTABLY SAFE. Toxicity of SOMA is extremely low. No effects on liver, endocrine system, blood pressure, blood picture or urine have been reported. Some patients may become sleepy on high dosage.

EASY TO USE. Usual adult dose is one 350 mg. tablet 3 times daily and at bedtime.

SUPPLIED: Bottles of 50 white sugar-coated 350 mg. tablets.
Literature and samples on request.

WALLACE LABORATORIES, NEW BRUNSWICK, N. J.

Collins Respirometer



It's a Metabolism Apparatus—a Vital Capacity Spirometer—and a Maximum Breathing Recorder. For the evaluation of cardio-pulmonary function, this new instrument is basic to the modern office or hospital, and it is as easy to use as any conventional BMR apparatus.

The Collins Vitalometer is only one of many spirometers designed especially for the study of respiration—Plastic, Timed, Recording, Box-Balloon, Double-Broncho and spirometers from one to 600 liters capacity.

MAIL COUPON FOR COMPLETE DETAILS

Warren E. Collins, Inc.
Specialists in Respiration Apparatus
555 Huntington Ave., Boston 15, Mass.

Gentlemen:
Please send me information on the equipment I have checked.

☐ Timed Vital ☐ Respirometer ☐ Double Broncho
☐ Tissot Gasometer ☐ Recording Vital ☐ 42 Page Catalog
☐ Box-Balloon Respirometer

Signed _____
Street _____
City _____ State _____

AJMS–6

2nd EDITION!

REDDISH-
Antiseptics, Disinfectants, Fungicides
and Chemical and Physical Sterilization

Edited by

GEORGE F. REDDISH, PH.D., SC.D. (HON.)
St. Louis College of Pharmacy and Allied Sciences; and Lambert-Hudnut Division of Warner-Lambert Pharmaceutical Company, St. Louis, Missori

28 CONTRIBUTORS
36 CHAPTERS
8 SUBJECT DIVISIONS

975 Pages. *67 Illustrations.*
134 Tables. *$15.00.*

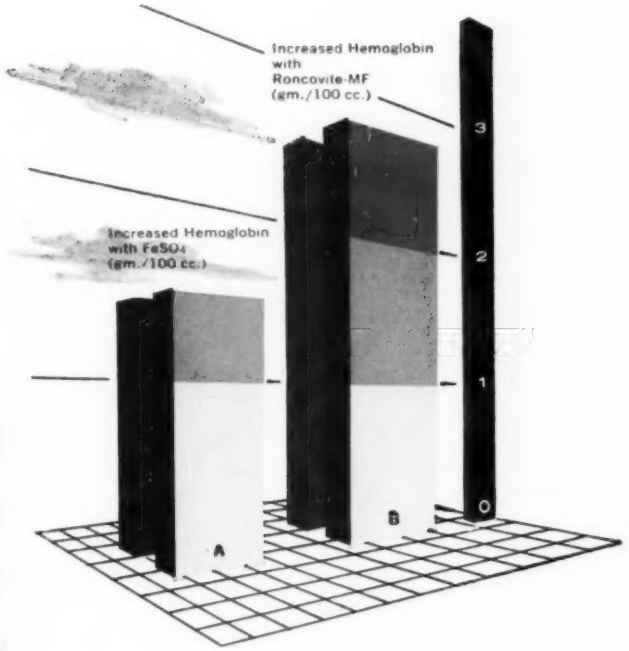
LEA & FEBIGER

WASHINGTON SQUARE
Philadelphia 6 Pennsylvania

LEGEND:

(A) Patients receiving ferrous sulfate 200 mg. q.i.d. showed average increase in hemoglobin of 1.5 gm.

(B) Patients receiving Roncovite-MF (15 mg. cobalt chloride and 100 mg. ferrous sulfate) showed average increase in hemoglobin of 2.7 gm.



Improved iron utilization in anemia

RONCOVITE®-mf

Each tablet contains: Cobalt chloride (Cobalt as Co....3.7 mg.)...15 mg. Ferrous sulfate, exsiccated...100 mg.

Improves iron utilization by enhancing the formation of erythropoietin, the erythropoietic hormone

Recent research[1,2] again emphasizes the role of cobalt as the only clinically proved agent which enhances erythropoietin formation.

The acceleration of erythropoiesis with Roncovite therapy provides optimal utilization of iron.

Acting through this physiologic mechanism, Roncovite (cobalt-iron) therapy results in an increased production of red cells and hemoglobin—a better blood picture—a faster, more complete response than iron alone in the common hypochromic anemias—menstrual anemia—anemia of pregnancy—nutritional anemia of infancy—and in anemia due to chronic infection or inflammation.[3,4,5,6,7,8]

(1) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L. F.: Blood *13*:55 (Jan.) 1958. (2) Gurney, C. W.; Jacobson, L. O., and Goldwasser, E.: Ann. Int. Med. *49*:363 (Aug.) 1958. (3) Korst, D. R.; Bishop, R. C., and Bethell, F. H.: J. Lab. & Clin. Med. *52*:364 (Sept.) 1958. (4) Ausman, D. C.: Journal-Lancet *76*:290 (Oct.) 1956. (5) Holly, R. G.: Obst. & Gynec. *9*:299 (Mar.) 1957. (6) Holly, R. G.: Clin. Obst. & Gynec. *1*:15 (Mar.) 1958. (7) Diamond, E. F.; Gonzales, F., and Pisani, A.: Illinois M. J. *113*:154 (April) 1958. (8) Hill, J. M.; La Jous, J., and Sebastian, F. J.: Texas J. Med. *51*:686 (Oct.) 1955.

LLOYD BROTHERS, INC. • **CINCINNATI 3, OHIO**

Coming This Summer!

In celebration of the
100th ANNIVERSARY of

GRAY'S ANATOMY

Lea & Febiger is proud to present
the fully up to date

AMERICAN CENTENNIAL (27th) EDITION

1859-1959

Anatomy of the Human Body. By HENRY GRAY, F.R.S. Edited by CHARLES MAYO GOSS, M.D., Managing Editor of the *Anatomical Record*; Professor and Head of the Department of Anatomy, Louisiana State University, New Orleans. About 1452 pages, 7″ × 10″. With 1174 illustrations, mostly in color. *New 27th (American Centennial) edition. Ready soon.*

WASHINGTON SQUARE **LEA & FEBIGER** PHILADELPHIA 6 PENNSYLVANIA

Proceedings of a Symposium on Experimental "Allergic" Encephalomyelitis and Its Relation to Other Diseases of Man and Animals

---

"ALLERGIC" ENCEPHALOMYELITIS

CONTRIBUTORS: **60 investigators from all over the world**—distinguished for significant work in pathology, immunology, neurology, and biochemistry.

- *They examine critically whether any or all of these can really be considered due to allergic reaction.*
- *They evaluate the possible relation of these disorders to each other and to other diseases, such as multiple sclerosis.*

PURPOSE: To assemble **all available data on** experimental "allergic" encephalomyelitis in a **readily accessible form** which would be of use to scientific workers in experimental neurology and related fields (neurochemistry, immunology and neuropathology). The material included will serve as a basis for future work on the pathogenesis and etiology of various neurological disorders.

Discussions built around twelve prepared speeches represent the heart of the book. **Authorities in other fields,** including most of those who have contributed to our knowledge of these diseases as well as many who are relatively unbiased by personal work in the field, participated. The discussions of each paper are recorded verbatim, edited to make readable, and brought up to date by many of the conferees since the symposium.

Here is the **newest information** concerning the etiology and pathogenesis of "allergic" encephalomyelitis, both as produced in experimental animals by injection of brain-containing vaccines and as occurring in man following injection of rabies-vaccine or other vaccines and following exanthematous or other infections.

Edited by

MARIAN W. KIES, Ph.D.
Chief, Section on Biochemistry, Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Maryland

and

ELLSWORTH C. ALVORD, Jr., M.D.
Associate Professor of Neurology and Pathology, Baylor University, College of Medicine, Houston, Texas

Publication date April, 1959
590 pages, 257 illustrations. $13.50

CHARLES C THOMAS • PUBLISHER
301–327 East Lawrence Avenue
Springfield • Illinois

THE MOST VEXING PROBLEM OF YOUR PRACTICE ANSWERED FULLY IN

Bonica—The Management of PAIN

With Special Emphasis on the Use of Analgesic Block in Diagnosis, Prognosis and Therapy

By JOHN J. BONICA, M.D.

Director, Department of Anesthesia, Tacoma General and Pierce County Hospitals, Clinical Associate, Department of Anatomy, University of Washington Medical School, Seattle

GUIDANCE FOR EVERY DOCTOR

Tells How to Relieve Distress Arising From Virtually Every Condition Which Causes Superficial to Intractable Pain

1533 Pages, 7" × 10". 785 Illustrations on 444 Figures. 52 Tables. $20.00

Washington Square — LEA & FEBIGER — Philadelphia 6 Pennsylvania

INDEX TO ADVERTISERS

Instruments and Apparatus

Sanborn Company 32
Warren E. Collins 196

Biologicals, Drugs & Pharmaceuticals

Ames Company 1
Astra Pharmaceutical Products, Inc. 17
Ayerst Laboratories 185
Brewer & Company 12
Eaton Laboratories 183
Endo Products 18
C. B. Fleet Co., Inc. 191
Flint-Eaton & Company ..... 2nd Cover
Geigy Pharmaceuticals 8, 189
Knoll Pharmaceutical Co. 10
Eli Lilly and Company 38
Lloyd Bros., Inc. 197
The S. E. Massengill Company 19, 20
Merck, Sharp & Dohme 6, 7, 26, 28, 29, 36, 37
Nordson Pharm. Laboratories, Inc. 15
Organon, Inc. 11
Chas. Pfizer Co., Inc. 21, 33, 34
Pitman-Moore Company ..... 3rd Cover
Riker Laboratories 35
A. H. Robins Co., Inc. 5
G. D. Searle & Company 13
E. R. Squibb & Sons, Div. of Olin-Mathieson Chemical Corp. 4, 184
R. J. Strasenburgh 186, 187
U.S. Vitamin Corp. 24, 25
Walker Laboratories 16
Wallace Laboratories 22, 23, 27, 194, 195
Winthrop Laboratories ..... 4th Cover
Wyeth Laboratories 9

Miscellaneous

International College of Surgeons 190

Publishers

Paul B. Hoeber, Inc. 188
Lea & Febiger 14, 196, 198, 200, 202
The C. V. Mosby Company 201
Charles C Thomas 199
The Williams & Wilkins Company 192

2

New Books to Provide You With Sound Clinical Advice on Extremity Cases

Just Published! DuVries

SURGERY OF THE FOOT

By **HENRI L. DuVRIES, M.D., B.Sc., D.S.C.,** Clinical Instructor in Surgery, Chicago Medical School; Attending Surgeon, Columbus Hospital, Mother Cabrini Hospital and Frank Cuneo Hospital, Chicago. Just Published. 494 pages, 6¾" × 9¾", 403 illustrations. Price, $12.50.

Here for the first time is a book which can help you improve your ability to treat all kinds of foot problems—from the minor ingrown nail to a major deformity such as the club foot. While other books deal mainly with the extreme disabilities, this practical volume covers the "minor" injuries, infections, burns and freezing, sprains, tumors and cysts, skin disorders, deformities and many other foot problems you are likely to encounter in your practice.

Dr. DuVries shows you how to examine the foot and make an accurate diagnosis; presents concise but detailed treatment in step-by-step form; and discusses general operative principles. In this practical volume, abundantly illustrated with more than 400 drawings, photographs and roentgenograms, you will find many of his procedures which have never appeared in published form before.

Soon-to-be-Released! Flatt

THE CARE OF MINOR HAND INJURIES

By **ADRIAN E. FLATT, M.A., M.D., F.R.C.S.,** Assistant Professor of Orthopedic Surgery, State University of Iowa. Ready next month. Approx. 250 pages, 6¾" × 9¾", 123 illustrations. About $9.00.

This new pocket-size book can be extremely valuable to every physician because it deals with "minor" hand injuries that can be safely treated on an out-patient basis. A "how-to-do-it" guide, this book explains in detail the treatment for all types of direct trauma to the hand, and burns, infections, bites, frostbite and other less common injuries. Although emphasizing "minor" hand injuries, the book has a wide application and covers such major procedures as the immediate replacement of skin loss.

Based on the author's personal experience in an out-patient clinic, this book classifies hand injuries and presents in detail, one safe, practical method of treatment for each injury. You will find this book well indexed for quick reference and well illustrated with actual case photographs that make it easy for you to match the case under treatment with the appropriate illustration in the book.

Purchase Any of Three Ways:

At Your Favorite Bookstore;
From Your Personal Representative;
Or Order on 10 Day Approval From

C V M **The C. V. Mosby Company**
3207 Washington Boulevard • St. Louis 3, Missouri

Physiology, Anatomy and Pathology of Gynecology
Correlated with Clinical Practice

Essentials of
Gynecology

By E. STEWART TAYLOR, M.D.
Professor and Head of the Department of Obstetrics and Gynecology,
University of Colorado School of Medicine, Denver

YOUNG practitioners of gynecology, undergraduate medical students and general practitioners will find this book to be a complete text and reference on the modern concepts of gynecology. Each chapter in this well-documented presentation is designed to meet the needs of the curriculum of modern medical schools. Fundamentals are presented in relation to clinical practice, with strong emphasis on gynecological pathology, physiology and endocrinology.

From history-taking to operation, Dr. Taylor explains the essentials of gynecology *clearly, concisely and fully.* Medical, surgical and irradiation treatments are taken up in relation to their advantages in the various conditions discussed. The more important gynecological surgical operations are presented step-by-step.

Other features include chapters on the adrenal gland, the pituitary gland, and preventive medicine, as they apply to gynecology. Each of these three subjects is believed to be presented for the first time in a book on this subject. The use of cortisone and sex steroids, pediatric gynecology, physiology of the menopause, and malignancies of the breast and other portions of the female body are detailed. Dr. Taylor emphasizes the importance of detection of malignant disease in its early stages and explains the proper procedure for breast examination by the physician as well as for self-examination by the patient. Infertility, use of endocrine preparations, abortion, stress incontinence, primary dysmenorrhea, total and radical hysterectomy, and fistula repair are among the many subjects considered.

The 343 illustrations include gross and miicroscopic photographs of conditions discussed in the text. Carefully made drawings aid readers to visualize principles and objectives of the most frequently used gynecologic operations.

502 Pages. *343 Illustrations and 7 in Color on 4 Plates.* *$12.00*

(Published June, 1958)

LEA & FEBIGER WASHINGTON SQUARE PHILADELPHIA 6 PA.

more dependable absorption for more predictable results in

HYPERTENSION

Protalba-R contains protoveratrine A,* a single alkaloid of veratrum for more effective management of the hypertensive patient.

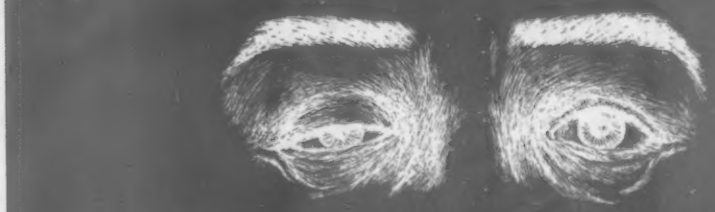
Protoveratrine A reduces elevated blood pressure with more predictable results than ever before possible in oral veratrum therapy because of its crystalline purity and ready absorption from the intestinal tract.

Combination of protoveratrine A with crystalline reserpine in Protalba-R permits blood pressure reduction with smaller and thus better tolerated doses than when either drug is used alone.

protalba-R†

†Trademark for Tablets Protoveratrine A, 0.2 mg. and Reserpine, 0.08 mg. *Patent Pending

PITMAN-MOORE COMPANY Division of Allied Laboratories, Inc., Indianapolis 6, Indiana



A GREAT STEP FORWARD

in the management of

MYASTHENIA GRAVIS

MYTELASE *chloride*

Brand of ambenonium chloride

(formerly Mysuran chloride)

Mytelase chloride (WIN 8077) is a new antimyasthenic compound with definite advantages over older cholinergics.

More pronounced improvement

Patients "... feel better, are stronger, and are closer to their normal health."[1]

More prolonged action

As a rule Mytelase "... has roughly twice the effectiveness per milligram of neostigmine in reducing the symptoms of myasthenia gravis, and approximately twice the duration."[2] Some patients can replace their former 10 to 60 tablets daily with as few as 2 tablets of Mytelase; sleep need not be interrupted for dosage.[1]

Fewer gastro-intestinal side effects

Supplied: Tablets, scored, of 10 mg. and 25 mg., bottles of 100.

Write for booklet discussing in detail clinical experience, dosage, side effects and precautions to be observed.

1. Schwab, R.S.; Marshall, Clare K.; and Timberlake, William: *J.A.M.A.*, 158:625, June 25, 1955.
2. Schwab, R.S.: *Am. Jour. Med.*, 19:734, Nov., 1955.

Mytelase, trademark

Winthrop LABORATORIES NEW YORK 18, N. Y.

9898